Appendix 3: Detailed clinical evidence tables

OIT PROTOCOL VARIABLES IN CLINICAL STUDIES OR PUBLISHED CLINICAL PRACTICE

	Allergen food preparation	Single starting dose in initial dose escalation	Build-up phase starting dose (per day)	Target dose (per day)	Up-dosing interval during build-up phase	Length of build-up phase (months)	Maintenance phase
Peanut							
RCTs with N> 50	**Peanut flour** (Anagnostou, 2014;[1] Blumchen, 2019;[2] Reier-Nilsen, 2019a[3]; Tang, 2015[4]), **AR101 powder** (Bird, 2018[5]; Vickery, 2018[6]) Adjuvant: *Lactobacillus rhamnosus CGMCC 1.3724* (Tang, 2015[4])	**0.1-0.5 mg PP** (Bird, 2018[5]; Tang, 2015[4]; Vickery, 2018[6])	**No initial dose escalation: 1-5 mg** (Anagnostou, 2014;[1] Reier-Nilsen, 2019a[3]) **0.1-30 mg PP** depending on eliciting dose (Blumchen, 2019[2]) **With initial dose escalation: 3 mg PP** (Vickery, 2018[6]) **6 mg PP** (Bird, 2018[5], **25 mg PP** (Tang, 2015[4])	**125 or 250 mg PP** depending on eliciting dose (Blumchen, 2019[2]) **300 mg PP** (Bird, 2018[5]; Vickery 2018[6]) **800 mg PP** (Anagnostou, 2014[1]) **2000 mg PP** (Tang, 2015[4]) **5000 mg PP** (Reier-Nilsen, 2019[3])	**2-3 weeks**	6 (Anagnostou, 2014[1]) 4.6 to 7.8 (Bird, 2018[5]) 13 median (range 10-14) (Blumchen, 2019[2]) 11.5 to 18.0 (Reier-Nilsen, 2019[3]) 8 (Tang, 2015[4]) ~6.4 (Vickery, 2018[6])	**5000 mg PP** daily for 36 months (Reier-Nilsen, 2019a[3]) **2000 mg PP** daily for 10 months (Tang, 2015[4]) **300 mg PP** daily for 24 weeks (Vickery, 2018[6]) **50-250 mg PP** daily; median (observed): 125 mg for 8±2 weeks (Blumchen, 2019[2])
Large case series	**Peanut flour**; **peanuts** for doses ≥ 300 mg PP (Nachshon, 2018[7]) **Peanut flour**; for higher doses **peanuts**, peanut butter, and other **processed peanut food products** (Wasserman, 2019[8]) **Peanut flour,** Bamba® (**peanut flour puffs**), **peanut butter powder compounded** at local pharmacies into capsules with inert filler (to be opened) (Soller, 2019[9])	**0.1 mg PP** (Nachshon, 2018[7]) **2.5 µg PP** (Wasserman, 2019[8]) **0.1 mg PP** (Soller, 2019[9])	**Median: 20 mg PP (IQR 7.5-100)** - single highest tolerated dose during initial dose escalation (Nachshon, 2018[7]) **Individualized** (Wasserman, 2019[8]) **No initial dose escalation: 10 to 12 mg PP** (Soller, 2019[9]) **With initial dose escalation:** individualized (Soller, 2019[9])	**3000 mg PP or ≥ 300 mg** for patients with difficulty reaching 3000 mg PP (Nachshon, 2018[7]) **3000 mg PP** (Wasserman, 2019[8]) **300-320 PP** (Soller, 2019[9])	**Monthly** (Nachshon, 2018[7]) **1-2 weeks** (Wasserman, 2019[8]) **2 weeks** (Soller, 2019[9])	8.7 median (IQR: 3.8 – 12.8) (Nachshon, 2018[7]) NR-Individualized (Wasserman, 2019[8]) 3.7 to 5.1 (16-22 weeks) (Soller, 2019[9])	**3000 or 1200 mg PP daily** for unlimited time (Nachshon, 2018[7]) **2000 mg of PP once or twice a day for** a minimum of 3 years (Wasserman, 2019[8]) **300-320 PP** (Soller, 2019[9])
Cow's milk							
RCTs with N> 50	**Milk**, diluted or whole (Longo, 2008;[10] Martorell, 2011;[11] Morisset, 2007;[12] de Schryver, 2019[13])	**0.5 mg CMP** (=0.017 mL milk) (Longo, 2008[10]) **0.3 mg CMP** (=0.010 mL milk) (De Schryver, 2019[13])	**≤ 20 mL** milk (individualized) (Longo, 2008[10]) **4 mL** milk (=120 mg CMP) (Martorell, 2011[11]) **1 mL** milk (=30 mg CMP) (Morisset, 2007[12])	**4500 mg CMP** (150 mL milk) (Longo, 2008[10]) **6400 mg CMP** (200 mL milk) (Martorell, 2011; De Schryver, 2019[13])	**2 days** (Longo, 2008[10]) **1 week** (Martorell, 2011;[11] Morisset, 2007;[12]) (De Schryver, 2019[13])	**12** (Longo, 2008[10]) **3.7** (Martorell, 2011[11]) **1.4** (Morisset, 2007[12])	**150 – 200 mL** milk daily plus dairy products ad libitum (Longo, 2008; [10] Martorell, 2011;[11] **200 mL/d** for 1 month, afterwards **≥200 mL twice a**

	Allergen food preparation	Single starting dose in initial dose escalation	Build-up phase starting dose (per day)	Target dose (per day)	Up-dosing interval during build-up phase	Length of build-up phase (months)	Maintenance phase
			2.5 mL (=75 mg CMP) De Schryver, 2019[13])	**7500 mg CMP** (250 mL milk) and dairy products (Morisset, 2007[12])			**week** plus dairy products ad libitum (De Schryver, 2019[13])
Large case series	**Powdered formula**; 3% fat **milk** for doses ≥ 90 mg of CMP (Levy, 2014[14]) **Milk** diluted in water (Kauppila, 2014[15])	**0.3 mg CMP** (=0.010 mL milk) (Levy, 2014[14])	**No initial dose escalation: 0.5 mg CMP** (=0.017 mL milk) (Kauppila, 2014[15]) **With initial dose escalation: Median 52.5 mg CMP** (=1.75 mL milk) (Levy, 2014[14])	**7200 mg CMP** (240 mL milk) (Levy, 2014[14]) **6400 mg CMP** (200 mL milk) (Kauppila, 2014[15])	**Monthly** (Levy, 2014[14]) **1-2 weeks** (Kauppila, 2014[15])	4-6 (Kaupilla, 2014[15])	4500 mg CMP daily (**150 mL milk**) plus ad libitum milk products for unlimited time (Elizur, 2016[16]) 6400 mg CMP daily (**200 mL milk**) for unlimited time (Kauppila, 2014[15])
Chicken's egg							
RCTs with N> 50	Dried egg white powder/ dehydrated egg white (Burks, 2012;[17] Escudero, 2015[18]) Powdered pasteurised egg (Fuentes-Aparicio, 2013[19]) Pasteurized egg white (Martin-Munoz, 2019a[20]) Hard-boiled egg (Morisset, 2007[12])	0.1 mg dried egg white powder (Burks, 2012[17]) 0.08 mg EWP (Escudero, 2015[18]) 1 mg powdered pasteurised egg (Fuentes-Aparicio, 2013[19]) 0.11 mg EWP (Martin-Munoz, 2019a[20])	3-50 mg dried egg white powder (individualized) (Burks, 2012[17]) 0.02 mg EWP (Escudero, 2015[18]) 30 mg powdered pasteurised egg (Fuentes-Aparicio, 2013[19]) Individualized, based on last tolerated dose in initial dose escalation (Martin-Munoz, 2019a[20]) 1 g of hard-boiled egg yolk (Morisset, 2007[12])	2 g of egg-white powder (~1/3 egg) (Burks, 2012[17]) 2.808 g EWP (Escudero, 2015[18]) 10 g powdered pasteurised egg (~1 egg) (Fuentes-Aparicio, 2013[19]) 30 mL pasteurized egg white (3.3 g EWP, ~1 egg) (Martin-Munoz, 2019a[20]) 4 g of egg yolk and 4 g of egg white plus foods containing eggs	**1-2 weeks** **Weekly plus daily or weekly only** (Martin-Munoz, 2019a)	10 (Burks, 2012[17]) 3 (planned), 1 (observed) (Escudero, 2015[18]) 3 (range 1.2-8.2) (Fuentes-Aparicio, 2013[19]) 2-3 (Morisset, 2007[12])	2 g of egg-white powder (~1/3 egg) daily for 12 months (Burks, 2012[17]) ≥ 1 undercooked egg every 2 days plus any other foods containing egg ad libitum (Escudero, 2015[18]) Normal, egg-containing diet (Fuentes-Aparicio, 2013[19]) 30 mL pasteurized egg white (3.3 g EWP, ~1 egg) daily or every 2 days (Martin-Munoz, 2019b[21])
Multi-food OIT							
Single-arm clinical study, Begin, 2014a[22] (N=40)	Food flours/powders (milk powder; egg powder; peanut, walnut, cashew, almond, pecan, hazelnut, pecan, wheat, soy, and sesame seed flours)	0.1 mg of each food allergen protein (i.e., 0.5 mg total food allergen protein for a patient with 5 allergies treated)	Highest tolerated dose at initial dose escalation (≤6 mg total food allergen protein) divided evenly among the treated food allergens	4000 mg food allergen protein per allergen (up to 20,000 mg for those with 5 allergies)	2 weeks	Individualized; median time to reach 1000 mg dose: approx. 16 months; 4000 mg:>20 months	4000 mg food allergen protein per allergen (i.e., 20,000 mg total food allergen protein for a patient with 5 allergies treated)
Single-arm clinical study, Begin, 2014b[23] (with omalizumab, N=25)		5 mg total food allergen protein divided evenly among the treated food allergens (e.g., 1 mg of each allergen for a patient with 5 allergies treated)	Highest tolerated dose at initial dose escalation (≤1250 mg total food allergen protein) divided evenly among the treated food allergens	4000 mg food allergen protein per allergen (up to 20,000 mg for those with 5 allergies)	2 weeks	Individualized; median time to reach maintenance dose was 4.14 months (range 1.6–8.3)	4000 mg food allergen protein per allergen

CMP: cow's milk protein; EWP: egg white protein; PP: peanut protein

Note: 1 peanut corresponds to approximately 250 mg peanut protein; 1 mL milk corresponds to 30 mg milk protein; 1 egg corresponds to 4g egg white protein or 30 mL pasteurized egg white or 6 g of egg-white powder

Summary table

Allergen food preparation	Adjuvants	Single starting dose in initial dose escalation	Build-up phase starting dose (per day)	Target dose (per day)	Up-dosing interval during build-up phase	Length of build-up phase (months)	Maintenance dose
Peanut: Peanut flour, AR101 powder, peanuts, peanut butter and other processed peanut products (e.g., peanut flour puffs), compounded peanut butter powder **Milk**: milk, diluted or whole; powdered (formula) **Egg**: Dried / dehydrated egg white powder; pasteurized egg white; hard-boiled egg **Multi-food OIT**: Food flours/powders	Lactobacillus, omalizumab	**Peanut:** 0.0025-0.5 mg peanut protein **Milk**: 0.3-0.5 mg milk protein **Egg**: 0.1-1 mg egg white powder or egg protein **Multi-food OIT**: 0.1 mg of each food allergen protein	**Peanut:** <u>No initial dose escalation:</u> 0.1-30 mg peanut protein <u>With initial dose escalation:</u> 3-100 mg peanut protein **Milk**: <u>No initial dose escalation:</u> 0.5 mg milk protein <u>With initial dose escalation:</u> 30-120 mg milk protein **Egg**: 0.02-50 mg egg white powder or egg protein	**Peanut:** 800 -5000 mg peanut protein (low dose OIT: 125-320 mg) **Milk**: 150-250 mL milk (4500-7200 mg milk protein) **Egg**: ~1 egg or ~1/3 egg **Multi-food OIT**: 4000 mg food allergen protein per allergen (up to 20,000 mg for those with 5 allergies)	Most common: 2-3 weeks; range: 2 days to 1 month	**Peanut**: 3.7 to 18 **Milk**: 1.4 to 12 **Egg**: 3 to 10 **Multi-food OIT:** No omalizumab median > 20 With omalizumab: 1.6-8.3, median 4.14	**Peanut:** 1200-5000 mg peanut protein /d (low dose OIT: 50-320 mg/d) **Milk:** 150-200 mL daily or at least twice weekly (4500-6500 cow milk protein) **Egg**: 3.3 g egg white protein (~1 egg) or 2 g of egg-white powder (~1/3 egg) or ≥ 1 undercooked egg daily or every 2 days

Protocols for other food allergens

	Nowak-Wegrzyn, 2019[24] (RCT, N=46) - wheat	Kulmala, 2018[25] (prospective, single-arm study, N=100) -wheat	Elizur, 2019[26] (CCT, N=73)-walnut	Barni, 2019[27] (case series, N=43) - hazelnut	Nachshon, 2019[28] (CCT) N=75 - sesame
Age	Median, 8.7 years; range, 4.2-22.3	Mean 11.6 years, range, 6.1-18.6	Mean 7.9 years OIT, 6.8 years control; range 4-20	Mean 10 years, range: 5-16	Mean 7.5 years, ≥4, (IQR: 5.8-11.6)
Diagnosis	DBPCFC	Open OFC (not performed in 15 patients with an immediate reaction within the previous 3 months)	OFC, unless an immediate, recent (past year) reaction was documented	OFC	OFC or reaction within past year together with positive skin prick test (SPT) result and/or specific serum IgE (>0.35 kUA/L)
OIT protocol	Biweekly escalation for up to 44 weeks to a maximum of 1445 mg of wheat protein (WP), followed by daily home maintenance dosing. After 52 weeks of treatment (≥ 8 weeks of maintenance dosing), DBPCFC for a cumulative dose of 7443 of WP (2-3 slices of bread). Subjects continued OIT for another year and underwent a year 2 DBPCFC and, if passed, a subsequent off therapy DBPCFC. Placebo-treated subjects crossed over to high-dose OIT (maximum, 2748 mg of WP).	Well-cooked wheat spaghetti was consumed every day for 17 weeks, increasing every 1-2 weeks from 0.3 to 2000 mg of wheat protein, followed by 3-month maintenance and 9-month follow-up Patients received antihistamine every day	Initial 4-day dose-escalation phase to establish the single highest tolerated dose, which was consumed daily at home for 24 days; subsequent monthly dose escalations were repeated until 4000 mg walnut protein was achieved. Patients who were desensitized to walnut continued to consume 1200 mg walnut protein daily for 6 months as maintenance.	Initial hospital OFC followed by hazelnut intake at home 3 times/ week with a dose equal to the maximum dose tolerated during hospital stay, up-dosing every 3 months at the hospital until 2.5 g hazelnut (cumulative dose) was reached	The initial 2 days of first dose-escalation round served as an entry OFC up to 4800 mg sesame protein (non-reacting patients were excluded). The single highest tolerated dose (SHTD) was then consumed at least once daily at home for 24 days. ubsequently, patients returned for monthly dose escalations performed in an ambulatory day care setting, Patients who could tolerate the target dose of 4000 mg sesame protein at the end build-up, were considered fully desensitized and were instructed to consume a daily maintenance dose of 1200 mg sesame protein (5g Tahini) plus ad-lib consumption of sesame products Patients who tolerated ≥ 240 mg sesame protein (~1 g of Tahini) but<4000 mg were considered partially desensitized and instructed to consume their achieved dose for an unlimited time

CLINICAL EFFICACY

Desensitization: increase in reactivity threshold

Data for peanut, milk and egg allergies

Meta-analyses			RCT not included in meta-analyses with N>50	
Nurmatov, 2017[29] – chicken's egg, cow's milk, peanut and others	**Romantsik, 2018[30] – chicken's egg**	**Chu, 2019[31] – peanut**	**Martin-Munoz, 2019a[20] (Spain) – chicken's egg** **N=101** **Age: 6-9 years** **Diagnosis confirmed with OFC: yes**	**De Schryver, 2019[13] (Canada) – cow's milk** **N=52** **Age: 6-18, mean 12.1 years** **Diagnosis confirmed with OFC: yes (single-blind)**
Desensitization in patients assessed in DBPCFC: All OIT trials - 17 RCTs[1,10-12,18,19,32-42] and 5 CCTs[43-47] **OIT: 75% (432/573)** **Control 11% (44/409)** RR (Control/OIT) = 0.14 (95% CI 0.08, 0.24) OIT RCTs only:[1,10-12,18,19,32-42] OIT: 71% (291/410) Control: 13% (43/334) RR (Control/OIT) = 0.18 (95% CI 0.10, 0.32) **- 5.55** Diagnosis confirmed by DBPCFC: OIT: 73% (412/565) Control: 13% (43/334) RR (Control/OIT) = 0.15 (95% CI 0.09, 0.27) **P<0.0001** Chicken's egg: - 9 RCTs[12,18,19,32,34,35,37,39,48] (1 SLIT[48]) and 1 CCT[47] **OIT: 74% (251/339)** **Control: 17% (36/208**), P<.0001 RR (Control/OIT) = 0.22 (95% CI 0.11, 0.45)	Induction of immunologic tolerance and/or ability to tolerate a full serving of egg as assessed in 9 RCTs[18,19,32,34,35,37,51-53] and 1 CCT:[54] **OIT: 45% (112/249)** **Control: 10% (19/190)** RR: 4.25 (95% CI 2.77, 6.53) *GRADE assessment: low quality of evidence* Ingestion of a partial serving of egg (1 g to 7.5 g) as assessed in 8 RCTs[18,19,32,34,35,37,51,53] and 1 CCT:[54] **OIT: 82% (192/234)** **Control: 10% (18/176)** RR= 7.48 (95% CI 4.91, 11.38) *GRADE assessment: low quality of evidence*	Passing an OFC at the highest dose tested (8 RCTs[1,2,4-6,42,55], 1 unpublished): • *Original analysis:* median cumulative dose 4250 mg PP (range 1043-5000 mg) = 17 (4.2-20) peanuts **OIT: 56% (320/574)** **Control: 3.2% (9/284)** RR=12.42 (95% CI 6.82, 22.61), P<.001 *GRADE assessment: High quality of evidence* • *Corrected analysis:* median cumulative dose 3022 mg PP (range 1043-5000 mg) = 12 (4.2-20) peanuts **OIT: 55% (315/574)** **Control: 2.8% (8/284)** **– see Section 8.1** *Alternative analysis: achieving at least partial desensitization:* passing an OFC with a cumulative dose of 400 to 5000 mg PP (1.6-20 peanuts) (median 2700 mg) across 8 RCTs[1,2,4-6,42,55] (1 unpublished): ***OIT: 73% (422/574)*** ***Control: 7.0% (21/284)***	Passing DBPCFC at 12 months with 3.3 g pasteurized raw egg white protein (cumulative) or reaching target dose of 3.3 g pasteurized raw egg white egg white protein (equivalent to 1 egg): **OIT: 84% (64/76)** **Control: 16% (4/25)** **P=0.000** *Cochrane risk of bias: high (MW assessment)*	OIT patients: reaching maintenance dose (200 mL) (8.8 g milk protein) Control patients: passing a single-blind OFC with a cumulative dose of 200 mL milk (8.8 g milk protein): **OIT: 69% (18/26)** **Control: 0 (0/26)** **Difference: 69% (95% CI: 48%, 91%)**

Meta-analyses			RCT not included in meta-analyses with N>50	
Nurmatov, 2017[29] – chicken's egg, cow's milk, peanut and others	**Romantsik, 2018[30] – chicken's egg**	**Chu, 2019[31] – peanut**	**Martin-Munoz, 2019a[20] (Spain) – chicken's egg** **N=101** **Age: 6-9 years** **Diagnosis confirmed with OFC: yes**	**De Schryver, 2019[13] (Canada) – cow's milk** **N=52** **Age: 6-18, mean 12.1 years** **Diagnosis confirmed with OFC: yes (single-blind)**
Cow's milk - 9 RCTs[10,11,33,36,38-41,48] (1 SLIT[48]) and 4 CCTs[43,44,46,47] – tolerance to median 45 to 250 mL (=1340-7500 mg milk protein) milk (median 200 mL=6000 mg) across trials **OIT: 78% (262/336)** **Control: 7.8% (15/193),** P<.0001 RR (Control/OIT) = 0.12 (95% CI 0.06, 0.25) Peanut - 2 OIT[1,42] and 2 SLIT[49,50] RCTs **OIT: 73% (65/89)** **Control: 3.7% (3/82),** P<.0001 RR (Control/OIT) = 0.11 (95% CI 0.04, 0.31)				

DBPCFC: double-blind, placebo-controlled food challenge; IQR: inter-quartile range; OFC: oral food challenge; OIT: oral immunotherapy; PP: peanut protein; RR: risk ratio; SLIT: sublingual immunotherapy
Note: approximate correspondence: 1 peanut = 250 mg peanut protein; 1 mL milk = 30 mg milk protein; 1 egg white=4g egg white protein
*An additional 15 patients continued to receive increasing amounts of cow milk at date of data cut-off (i.e., had not completed the build-up phase).

Case series (clinical practice) with N>150				
Levy, 2014[14] (Israel)– cow's milk **N=265*** **Age: 4-27 (7.5 median) years** **Diagnosis confirmed with OFC: not for all patients**	**Kauppila, 2019[15] (Finland) – cow's milk** **N=295** **Age: 5-17 (median 7.5) years** **Diagnosis confirmed with OFC: yes**	**Soller, 2019[9] (Canada) – peanut** **N=270** **Age: 0.75-5.9 (median 1.9, IQR : 1.25-2.75) years** **Diagnosis confirmed with OFC: for 31% of patients**	**Wasserman, 2019[8] (USA) – peanut** **N=270** **Age: 4-18 (mean: 8.1) years** **Diagnosis confirmed with OFC: no**	**Wasserman, 2014[56] (USA and Israel)-peanut** **N=352** **Age: 3-24 years** **Diagnosis confirmed with OFC: 97% of patients**
Completion of treatment program and ability to freely consume milk or milk products (> 7.2 g milk protein): **60%** (160/265) Ability to tolerate ≥ 180 mg of milk protein (6 mL of milk): **85%** (226/265)	Consuming ≥200 mL/d of milk (6.4 g milk protein) 3 months after reaching the maintenance dose of 200 mL: **71%** (209/295); Consuming <200 mL (10-190 mL): 18% (54/295) *Consuming ≥ 10 mL milk: 89% (263/295)* Avoiding milk consumption: or lost to follow-up: 11% (32/295)	Reaching the target maintenance dose of 300-320 mg PP (1.2-1.3 peanuts): **90%** (243/270)	Reaching the target dose of 3000 mg PP: **78%** (211/270) (an additional 3 patients reached a planned target dose of 2000 mg PP) Passing an OFC with 6000 mg PP: **78%** (210/270)	Reaching the target dose of 415-8000 mg PP: **85%** (298/352)

DBPCFC: double-blind, placebo-controlled food challenge; IQR: inter-quartile range; OFC: oral food challenge; OIT: oral immunotherapy; PP: peanut protein; RR: risk ratio

Note: approximate correspondence: 1 peanut = 250 mg peanut protein; 1 mL milk = 30 mg milk protein; 1 egg white=4g egg white protein

*An additional 15 patients continued to receive increasing amounts of cow milk at date of data cut-off (i.e., had not completed the build-up phase).

Data for other food allergies

	Nowak-Wegrzyn, 2019[24] (RCT, N=46) -wheat	**Kulmala, 2018[25] (prospective, single-arm study, N=100) -wheat**	**Elizur, 2019[26] (CCT, N=73)-walnut**	**Barni, 2019[27] (case series, N=43) - hazelnut**	**Nachshon, 2019[28] (CCT) N=75 - sesame**
Age	Median, 8.7 years; range, 4.2-22.3	Mean 11.6 years, range, 6.1-18.6	Mean 7.9 years OIT, 6.8 years control; range 4-20	Mean 10 years, range: 5-16	Mean 7.5 years, ≥4, (IQR: 5.8-11.6)
Diagnosis	DBPCFC	Open OFC (not performed in 15 patients with an immediate reaction within the previous 3 months)	OFC, unless an immediate, recent (past year) reaction was documented	OFC	OFC or reaction within past year together with positive skin prick test (SPT) result and/or specific serum IgE (>0.35 kUA/L)
Desensitization	At year 1, 12/23 (52%) low-dose VWG OIT-treated and none of 23 placebo-treated subjects consumed successfully ≥ 4443 mg of WP (primary end point) (P < .0001); median doses successfully consumed were 4443 and 143 mg, respectively. Among placebo-treated subjects who crossed over to high-dose VWG OIT, 12/21 (57%) were desensitized after 1 year (median dose, 7443 mg of WP; nonsignificant vs low-dose VWG OIT).	At the end of the 17-week build-up period, 64% (64/100) patients reached the target dose of 2000 mg /d WP (24 strands of spaghetti). Among the remaining 36 patients (including 23 who had discontinued), the median maximum tolerated dose was 5.5 strands of spaghetti (445 mg WP, range 1–1760) After 3 month maintenance, 47 patients consumed 2000 mg/d WP, 25 consumed a median of 330 mg (range 5–1750) and 5 had discontinued	Passing an OFC with 4000 mg of walnut protein (26-g walnut): 49/55 (89%) patients in the OIT group compared to 0/18 patients in the control group (odds ratio 9·2, 95% CI 4·3–19·5; P<.0001). Nine (50%) control patients began walnut OIT, and 7 (78%) were desensitized to 4000 mg walnut protein All patients who were co-allergic to pecan (n=46) were also desensitized to pecan. Additionally, 18/30 (60%) patients who were co-allergic to hazelnut or cashew, and 14/15 (93%) patients who were co-allergic to hazelnut alone, were either fully desensitized or responded to treatment.	65% (28/43) reached the cumulative dose of 2.5 g hazelnut (0.375 g hazelnut protein) 35% (15/43) ongoing, tolerating a mean dose of 255 mg hazelnut Average time to complete treatment was 5 months (range 3-12)	Full desentiziation (4000 mg sesame protein): 88% (53/60) vs 0% (0/15) (median time to achieving maintenance dose was 6.5 (IQR, 3.8-12.8) months) At least partial desentiziation (≥ 240 mg sesame protein): 100% (60/60) vs 0% (0/15) Control (eligible, but did not undergo OIT due to non-clinical reasons, eg., long distance from clinic): 0% (0/15)

DBPCFC: double-blind, placebo-controlled food challenge; SCD: successfully consumed dose; VWG: vital wheat gluten

Note: 7 walnuts correspond to approx. 28.3 g (1 ounce serving); 12 hazelnuts correspond to approx. 28.3 g (1 ounce serving), with 1 hazelnut weighting about 2.4 g

Assessment of the quality of evidence

		Risk of bias (Cochrane tool[57] for interventional comparative studies; IHE tool[58] for case series)	**Level of evidence (Oxford Centre for Evidence-based medicine) -** adapted using the approach of the European Academy of Allergy and Clinical Immunology[59]
Peanut	**Interventional comparative studies (RCTs, CCTs):** Chu meta-analysis (8 RCTs[1,2,4-6,42,55], 1 unpublished)	**Low -** 8 RCTs of which 5 were rated as being at low risk of bias and 3 as high risk of bias for this outcome*	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: Soller, 2019[9], Wasserman, 2019,[8] Wasserman, 2014[56]	**Moderate** – 3 case series: 2 with retrospective study design; 1 single center; OFC as outcome in 1 study only	
Egg	**Interventional comparative studies (RCTs, CCTs):** Romantsik, 2018[30] meta-analysis (9 RCTs[18,19,32,34,35,37,51-53] and 1 CCT[54]) plus 1 RCT (Martin-Munoz, 2019a[20])	**High** – All RCTs rated as being at overall high risk of bias by ≥1 analysis	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series	**--**	
Milk	**Interventional comparative studies (RCTs, CCTs):** meta-analysis (9 RCTs[10,11,33,36,38-41,48] (1 SLIT[48]) and 4 CCTs[43,44,46,47]) plus 1 RCT (De Schryver, 2019[13])	**High** – meta-analysis: of the 9 RCTs, 5 were rated as being at high risk of bias and 2 at unclear risk of bias; RCT not in meta-analysis- high risk of bias	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: Levy, 2014[14] and Kauppila, 2019[15] (clinical practice)	**Moderate** – 2 case series from clinical practice, main limit: retrospective study design, no OFC as outcome; 1 was conducted at a single center	
Wheat	**Interventional comparative studies (RCTs, CCTs)**: Nowak-Wegrzyn, 2019[24]	**Low** – 1 RCT	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: 1 prospective case series in research context (Kulmala, 2018[25])	**Low** – 1 prospective case series	
Walnut	**Interventional comparative studies (RCTs, CCTs)**: Elizur, 2019[26] (CCT, N=73)	**High** – non-randomized control group,** unblinded	Level II two groups, non-randomized studies
	Case series: NA		
Hazelnut	**Interventional comparative studies (RCTs, CCTs)**:NA	**--**	Level III: one group non-randomized
	Case series: Barni, 2019[27] (clinical practice)	**High** - 1 case series from clinical practice, limits: retrospective study design, single center, unclear recrutement and eligibility criteria	
Sesame	**Interventional comparative studies (RCTs, CCTs)**: Nachshon, 2019[28]	**High** – non-randomized control group,*** unblinded	Level II two groups, non-randomized studies
	Case series: NA	**--**	

*Note: Sensitivity analyses that adjusted for risk of bias yielded similar results to the main analysis (Chu et al, 2019[31]).

** Treatment assignment was based on the order in which patients presented at to the clinic, with the first patients starting OIT and the remain ing patients being managed by observation and strict dietary exclusion (control group).

*** Controls were patients eligible for OIT but refrained from treatment during the study period for nonmedical reasons, such as a large travel distance to the clinic or previous obligations at the time of their invite to treatment.

Continued allergen food consumption

Data for peanut, milk and egg allergies

LTFU of RCTs (with control arm data)			Large case series (N≥145)		
Jones, 2016[60] – LTFU of Burks, 2012 (egg)[32] Diagnosis confirmed with OFC: no	**Hsiao, 2017[61] – LTFU of Tang 2015 (peanut):[4]** Diagnosis confirmed with OFC: no	**Meglio, 2017[62] – LTFU of Meglio 2013 (egg)[37]** Diagnosis confirmed with OFC (DBPCFC)	**Kauppila, 2019[15] (Finland) – cow's milk** N=295 Age: 5-17 (median 7.5) years Diagnosis confirmed with OFC	**Elizur, 2016[16] (Israel) - cow's milk** N=196 Age: >6, mean 10 years Diagnosis confirmed with OFC for patients without an anaphylactic reaction in the preceding year	**Nachshon, 2018[7] (Israel)- peanut*** N=145 Age: ≥4 (median 5.8) years Diagnosis confirmed with OFC for patients without an anaphylactic reaction in the preceding year
Patients followed: All patients who started OIT or control therapy **Follow-up**: Point 1: approx. 5 years after study enrolment; Point 2: 1 year later **Completeness of follow-up**: OIT: 85% (34/40); placebo: 73% (11/15) at both time points <u>Among patients with follow-up:</u> **Eating baked or unbaked egg:** At point 1: OIT: 82% (28/34) vs placebo: 36% (4/11), P=.007; At point 2: OIT: 85% (28/33) vs placebo: 67% (8/12), P=.22 **Eating baked and unbaked egg:** At point 1: OIT: 68% (23/34) vs placebo: 18% (2/11), P=.006; At point 2: OIT: 64% (21/33) vs placebo: 25% (3/12), P=.04 *Sensitivity analysis (all lost to FU assumed to avoid):* *At point 1:* *OIT: 58% (23/40) vs placebo: 13% (2/15);*	**Patients followed:** All patients who started OIT or control therapy **Follow-up:** Mean of 4.2 years (SD 0. 7) from treatment cessation **Completeness of follow-up**: 77% (OIT: 24/31; placebo: 24/31) of patients <u>Among patients with follow-up:</u> **Eating peanuts:** OIT: 67% (16/24) vs Control 4.2% (1/24) P=.001 *Sensitivity analysis (all lost to FU assumed to avoid):* *OIT: 52% (16/31) vs Control 3.2% (1/31)* **Eating peanuts at least weekly:** OIT: 46% (11/24) vs Control 4.2% (1/24) P=NR *Sensitivity analysis (all lost to FU assumed to avoid):* *OIT: 35% (11/31) vs Control 3.2% (1/31)* **Eating > 2000 mg PP:**	**Patients followed:** All patients who started OIT or control therapy **Follow-up:** Mean of 2.5 (SD 0.3) and 7 (SD 0.9) years after original study start **Completeness of follow-up**: 2.5 years: 9/10 OIT, 10/10 control; 7 years: 9/10 OIT, 9/10 control <u>Among patients with follow-up:</u> **Being able to eat raw and/or cooked egg at least once a week without symptoms:** OIT group: 7/9 children (78%) at both time points Control: 2.5-year FU: 3/10 (30%), P<.05; 7-year FU: 3/9 (33%), P=n.s. (2 control children started OIT) *Sensitivity analysis (all lost to FU assumed to avoid):* *OIT: 70% (7/10) vs Control 30% (3/10)*	**Patients followed:** All patients who started OIT **Follow-up**: median 6.5 years (range 1-11) **Completeness of follow-up**: 83% (244/295) of patients <u>Among patients with follow-up:</u> **Consuming ≥200 mL milk/d:** 56% (136/244) – *SA: 46% (136/295)* **Consuming ≥200 mL milk/d with no self-reported milk-related side effects in the last year:** 26% (77/244) **Consuming <200 mL (10-190 mL) milk/d:** 18% (44/244) **Avoiding milk consumption**: 26% (65/244) of patients **Any milk consumption** (≥ 10 mL/d)**:** 74% (180/244) *Sensitivity analysis (all lost to FU assumed to avoid): 61% (180/295)*	**Patients followed:** Patients who reached full cow milk protein consumption **Follow-up**: ≥ 6 months after completing build-up phase; median: 24.8 (range 6–41) months **Completeness of follow-up**: 195/196 (99%) of patients <u>Among patients with follow-up:</u> **Consuming ≥ 4.5 g of cow milk protein ≥3 times per week**: 93% (181/195) of patients *Sensitivity analysis (all lost to FU assumed to avoid): 92% (181/196)* **Discontinued milk consumption**: 7.2% (14/195) of patients	**Patients followed:** All patients who started OIT **Follow-up:** ≥ 6 months after completing build-up phase; median: 18 (range 6–75) months **Completeness of follow-up**: 142/145 (98%) of all patients 130/133 (98%) of patients reaching 3000 mg (n=113) or 300-2400 mg (n=20) PP at end of up-dosing **Eating peanuts regularly (≥300 mg peanut protein/d)**: All patients with follow-up: 113/142 patients (80%) *Sensitivity analysis (all lost to FU assumed to avoid): 78% (113/145)* Patients who reached maintenance: 87% (113/130) *Sensitivity analysis (all lost to FU assumed to avoid): 85% (113/133)* **Discontinued eating peanuts** (among patients who reached maintenance): 17/130 (13%)

LTFU of RCTs (with control arm data)			Large case series (N≥145)		
Jones, 2016[60] – LTFU of Burks, 2012 (egg)[32] Diagnosis confirmed with OFC: no	**Hsiao, 2017[61] – LTFU of Tang 2015 (peanut):[4]** Diagnosis confirmed with OFC: no	**Meglio, 2017[62] – LTFU of Meglio 2013 (egg)[37]** Diagnosis confirmed with OFC (DBPCFC)	**Kauppila, 2019[15] (Finland) – cow's milk** N=295 Age: 5-17 (median 7.5) years Diagnosis confirmed with OFC	**Elizur, 2016[16] (Israel) - cow's milk** N=196 Age: >6, mean 10 years Diagnosis confirmed with OFC for patients without an anaphylactic reaction in the preceding year	**Nachshon, 2018[7] (Israel)- peanut*** N=145 Age: ≥4 (median 5.8) years Diagnosis confirmed with OFC for patients without an anaphylactic reaction in the preceding year
At point 2: OIT: 53% (21/40) vs placebo: 20% (3/15) 20 OIT patients had demonstrated SU at some point over 4 years of treatment; 18 of them responded to the FU survey and all (100%) reported consumption of all forms of egg at points 1 and 2.	OIT: 52% (12/23) Placebo: 4% (1/24) P=.001 23 OIT patients had demonstrated SU at 18 months of treatment; 20 of them responded to the FU survey. 16/20 (80%) reported regular consumption of peanuts at FU, 1 had discontinued due to taste aversion and 3 failed subsequent DBPCF				**Reasons for discontinuation**: food aversion (13/17), treatment burden (3/17), heartburn (1/17) **Failed OIT (did not reach maintenance dose):** 12/142 (8.5%)

PP: peanut protein

Data for other food allergies

	Nowak-Wegrzyn, 2019[24] (RCT, N=46) -wheat	**Kulmala, 2018[25] (prospective, single-arm study, N=100) -wheat**	**Elizur, 2019[26] (CCT, N=73)-walnut**	**Barni, 2019[27] (case series, N=43) - hazelnut**	**Nachshon, 2019[28] (CCT) N=75 - sesame**
Age	Median, 8.7 years; range, 4.2-22.3	Mean 11.6 years, range, 6.1-18.6	Mean 7.9 years OIT, 6.8 years control; range 4-20	Mean 10 years, range: 5-16	Mean 7.5 years, ≥4, (IQR: 5.8-11.6)
Diagnosis	DBPCFC	Open OFC (not performed in 15 patients with an immediate reaction within the previous 3 months)	OFC, unless an immediate, recent (past year) reaction was documented	OFC	OFC or reaction within past year together with positive skin prick test (SPT) result and/or specific serum IgE (>0.35 kUA/L)
Long-term follow-up	No data	After 9 month maintenance: 39/100 consumed ≥2000 mg/d WP 18/100 consumed a median of 500 mg (range 83–1000) WP (1-12 strands of spaghetti) 43/100 had discontinued	45 of 56 patients who had been desensitized to walnut had follow-up data (≥ 6 months after end of OIT) and were consuming a daily dose of 1200 mg walnut protein – 70% (45/64) of patients who had initiated OIT	At 1-year follow-up, all patients who had completed treatment continued to consume hazelnut, at a dose of ≤ 2.5 g ≥ 1 time a week, without adverse reactions	Follow-up ≥6 months after reaching the maintenance dose (median 8, range 5.5-34.6) months Completeness of FU: 100% (56/56-4 patients had not yet reached ≥6 months) for regular consumption, 82% (46/56) for OFC Regular consumption (ITT analysis): ≥1200 mg sesame protein : 88% (49/56) ≥480 mg sesame protein : 93% (52/56) OFC with 4000 mg sesame protein: 82% (46/56)

Assessment of the quality of evidence

		Risk of bias (Cochrane tool[57] for interventional comparative studies; IHE tool[58] for case series)	**Level of evidence (Oxford Centre for Evidence-based medicine) -** adapted using the approach of the European Academy of Allergy and Clinical Immunology[59]
Peanut	**Interventional comparative studies (RCTs, CCTs)** *- Hsiao, 2017[61]*	**High**- 1 LTFU on RCT, limitations: open-label and loss to follow-up	Level II two groups, non-randomized studies
	Case series - *Nachshon, 2018[7]*	**Moderate –** 1 case series; main limits: single-center, retrospective data collection	
Egg	**Interventional comparative studies (RCTs, CCTs) -** *Jones 2016[60], Meglio 2017[62]*	**High** - 2 LTFU on RCTs, limitations: open-label and loss to follow-up	Level II two groups, non-randomized studies
	Case series	**--**	
Milk	**Interventional comparative studies (RCTs, CCTs):**	**--**	Level III: one group non-randomized
	Case series: **-** *Kauppila 2019[15], Elizur 2016[16]*	**Moderate** – 2 large case series; main limits: single-center, retrospective data collection	
Wheat	**Interventional comparative studies (RCTs, CCTs)**	**--**	Level III: one group non-randomized
	Case series: 1 prospective case series in research context (Kulmala, 2018[25])	**Low** – 1 prospective case series of low risk of bias	
Walnut	**Interventional comparative studies (RCTs, CCTs)**: Elizur, 2019[26] (CCT, N=73)	**High** – non-randomized control group,** unblinded	Level II two groups, non-randomized studies
	Case series: NA		
Hazelnut	**Interventional comparative studies (RCTs, CCTs)**:NA	**--**	Level III: one group non-randomized
	Case series: Barni, 2019[27] (clinical practice)	**High -** 1 small case series from clinical practice, limits: retrospective study design, single center, unclear recruitment and eligibility criteria and follow-up	
Sesame	**Interventional comparative studies (RCTs, CCTs)**: Nachshon, 2019[28]	**High** – single-arm follow-up, unblinded	Level III: one group non-randomized

Sustained unresponsiveness

Data for peanut, milk, egg allergies

Meta-analyses : Nurmatov, 2017[29]
Ability to safely consume foods containing the allergen in question after discontinuing as assessed in 3 egg RCTs (Burks 2012,[32] Caminiti, 2015,[34] Escudero, 2015,[18]) and 1 milk/egg RCT (Staden, 2007[41]) with DBPCFC - approx. 88% of patients were treated for egg allergy, period of avoidance was 1-3 months across studies **OIT: 34%** (36/113) **Control: 11%** (9/81) RR (Control/OIT)=0.29 (95% CI 0.08, 1.13) P < 0.074

DBPCFC: double-blind controlled food challenge

RCTs (N≥50) not included in meta-analyses

Study	**Age (years)**	**Design**	**Intervention (N initiated treatment)**	**Comparator (N initiated treatment)**	**Allergy confirmed with DBPCFC?**	**Interval between treatment initiation and SU assessment**	**Intervening period of allergen avoidance**	**SU assessment**	**SU – ITT analysis**
Sampson, 2019 [abstract],[63] USA – **egg***	Mean 8 (range 3.5–16.8)	RCT	OIT (N=23)	Baked egg products consumption (N=27)	Yes	24 months (2 years)	8-10 weeks	DBPCFC - 7.4 g egg-white protein (1.9 egg whites), cumulative	44% (10/23) vs 11% (3/27), P=.009
Tang, 2015,[4] (*OIT with probiotic Lactobacillus*) Australia – **peanut**	Mean 6 (SD 2.4)	Double-blind, placebo-controlled RCT	OIT + probiotic (Lactobacillus rhamnosus CGMCC 1.3724) (N=31)	Placebo (N=31)	For a subset of participants	18 months	2-5 weeks	DBPCFC -2 g peanut protein (8 peanuts), cumulative	74% (23/31) vs 3.2% (1/31), P=0.001

**Even though this study was published only as abstract, it was included for the SU endpoint due to scarcity of data on SU (data reporting validated by checking data posted on Clinical trials.gov)*
Note: 1 egg white contains about 4 g of protein; 1 peanut contains about 250 mg of protein

Case series and prospective cohort studies (single arm)

- Wasserman, 2019[8] (case series, N=270) – peanut: Patients were invited to test for SU if they had ≥ 36 months of maintenance dosing (a total of 105 patients), no ETRs within 2 years, ≥ 90% fall in peanut-specific IgE level or a prechallenge peanut-specific IgE < 1.0 kU/mL. After an avoidance period of 1 month, 19 patients were challenged (including 8 who did not meet these criteria) with 6 g peanut protein (24 peanuts); 74% (14/19) passed – among all patients who had ≥ 36 months of maintenance dosing: **13% (14/105)**
- Vickery, 2014[64] (prospective cohort studies, age 1-16 years) – peanut: Of the 39 subjects originally enrolled, 12 (31%, 12/39) successfully passed a challenge with 5000 mg of peanut protein one month after stopping OIT.

ADDITIONAL EVIDENCE

Smaller RCTs, CCTs or retrospective case-control studies (ITT analyses)

Study	Design	Food allergen	Intervening period of allergen avoidance	SU – ITT analysis	
				OIT	Comparator
Nagakura, 2018[65], low-dose OIT	Prospective cohort study with historical control	Peanut	2 weeks	33% (8/24)	Historical controls: 0 (0/23)
Narisety 2015[66]	RCT	Peanut	4 weeks	27% (3/11)	SLIT 10% (1/10)
Takahashi, 2016[67]	CCT	**Milk**	2 weeks	21% (7/31) – 1 year 45% (14/31) -2 years	Untreated: 0/17 (1 year)
Vickery, 2017,[68] USA age 9-36 months	RCT comparing different maintenance doses with a substudy that retrospectively identified and matched standard of care controls	Peanut	4 weeks	85% (17/20) low dose maintenance 71% (12/17) high dose maintenance, Overall: 78% (29/37)	Historical matched controls: 3.9% (6/154), P<0.001
Yanagida 2016[69], low-dose OIT	RCT	Egg	2 weeks	71% (15/21) – 1/32 of one whole egg 33% (7/21) - 1/2 of one whole egg	Control: 0 (0/12) for both outcomes

Allergens other than milk, egg and peanut

	Nowak-Wegrzyn, 2019[24] (RCT, N=46) -wheat	**Kulmala, 2018[25] (prospective, single-arm study, N=100) -wheat**	**Elizur, 2019[26] (CCT, N=73)-walnut**	**Barni, 2019[27] (case series, N=43) - hazelnut**	**Nachshon, 2019[28] (CCT) N=75 - sesame**
Age	Median, 8.7 years; range, 4.2-22.3	Mean 11.6 years, range, 6.1-18.6	Mean 7.9 years OIT, 6.8 years control; range 4-20	Mean 10 years, range: 5-16	Mean 7.5 years, ≥4, (IQR: 5.8-11.6)
Diagnosis	DBPCFC	Open OFC (not performed in 15 patients with an immediate reaction within the previous 3 months)	OFC, unless an immediate, recent (past year) reaction was documented	OFC	OFC or reaction within past year together with positive skin prick test (SPT) result and/or specific serum IgE (>0.35 kUA/L)
Sustained unresponsiveness	At year 2, 7/23 (30%) low-dose VWG OIT-treated subjects were desensitized to 7443 mg of WP **At year 2, 3/23 (13%) low-dose VWG OIT-treated subjects achieved SU 8 to 10 weeks off therapy to (SCD, 7443 mg of WP in DBPCFC)**	NA	**No data on** SU - (45 of 56 patients who had been desensitized to walnut had follow-up data (≥ 6 months after end of OIT) all of them (100%) maintained walnut desensitization for ≥6 months after reaching maintenance (passed OFC with single dose of 4000 mg walnut protein) – 70% (45/64) of patients who had initiated OIT)	NA	NA

DBPCFC: double-blind, placebo-controlled food challenge; SCD: successfully consumed dose; VWG: vital wheat gluten

Note: 7 walnuts correspond to approx. 28.3 g (1 ounce serving); 12 hazelnuts correspond to approx. 28.3 g (1 ounce serving), with 1 hazelnut weighting about 2.4 g

Assessment of the quality of evidence

		Risk of bias (Cochrane tool[57] for interventional comparative studies; IHE tool[58] for case series)	**Level of evidence (Oxford Centre for Evidence-based medicine) -** adapted using the approach of the European Academy of Allergy and Clinical Immunology[59]
Peanut	**Interventional comparative studies (RCTs, CCTs)** *- Tang 2015[4]*	**Low**- 1 RCT considered at low risk of bias	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series – Wasserman, 2019[8]	**High –** 1 case series; main limits: single-center, retrospective data collection, only a small proportion of patients was assessed for SU	
Egg	**Interventional comparative studies (RCTs, CCTs) – meta-analysis (88% /12% milk):** *including Burks 2012,[32] Caminiti, 2015,[34] Escudero, 2015, Staden, 2007[41]) **	**Moderate** – 4 RCTs, of which at least 2 are considered being at high risk of bias	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series	**--**	
Milk	**Interventional comparative studies (RCTs, CCTs):** Takahashi, 2016[67]	**High** – 1 small open-label CCT**	Level II two groups, non-randomized studies
	Case series: **-** NA	**--**	
Wheat	**Interventional comparative studies (RCTs, CCTs):** Nowak-Wegrzyn, 2019[24]	**Medium** – 1 small RCT with no control data	Level III: one group non-randomized
	Case series: NA	**--**	
Walnut	**Interventional comparative studies (RCTs, CCTs)**	**--**	
	Case series: NA	**--**	
Hazelnut	**Interventional comparative studies (RCTs, CCTs)**:NA	**--**	
	Case series: NA	**--**	
Sesame	**Interventional comparative studies (RCTs, CCTs)**: NA	**--**	
	Case series: NA	**--**	

*The quality of the study published in abstract form only (Sampson, 2019[63]) was not assessed

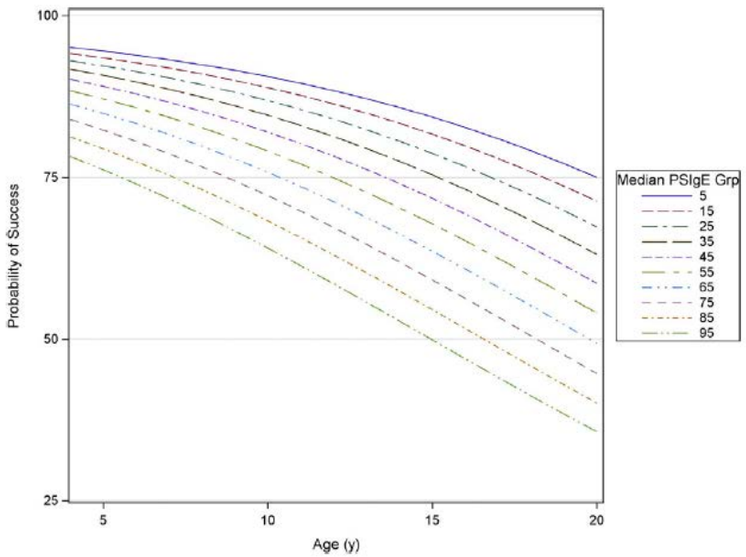
** The control group were patients who did not want to undergo OIT

Impact of patient characteristics on efficacy outcomes

- Most OIT studies enrolled children and adolescents starting from age 4 to 7 years, with median/mean ages in the range of 6 to 12 years (Anagnostou, 2014;[1] Bird, 2018;[5] Burks, 2012;[32] Elizur, 2016;[16] Escudero,2015;[18] Fuentes-Aparicio, 2013;[19] Kauppila, 2019;[15] Levy, 2014;[14] Longo, 2008;[10] Martin-Munoz, 2019;[20] Nachshon, 2018;[7] Reier-Nilsen, 2019;[3] Vickery, 2018[6] and Wasserman, 2019[8]). Three studies enrolled peanut-allergic children starting from a younger age, three years (Blumchen, 2019;[2] Wasserman, 2014[56]) or one year (Tang, 2015[4]). One study enrolled children for milk or egg OIT starting from the age of one year (Morisset, 2007[12]).

- **Older children, adolescents and adults**

- Association between baseline age and likelihood of achieving efficacy outcomes in large case series of children and adolescents (N: 145 to 295):
    i. Wasserman (2019[8]) reported (based on multivariate analysis) that among a cohort of 270 **4- to 18**-year old children and adolescents with **peanut** allergy (mean age 8.1 years), older age at the initiation of therapy significantly reduced the likelihood of reaching the target maintenance dose by 17% for each year after the age 5 years (odds ratio 0.83 [95% CI 0.75-0.93], P< .001) (see figure below).



    ii. Other case series did not find such an association:
        1. Kauppila (2019[15]) observed (based on logistic regression analysis) that baseline age (<7 versus ≥7 years) was **not** a statistically significant predictor of treatment failure among 296 patients **5 to 17** years of age (median **7.5**) undergoing **milk** OIT.
        2. Levy (2014[14]) reported that among 280 **4- to 27**-year old patients (median **7.5** years) undergoing **milk** OIT there was no difference in median age between those who did or did not achieve the full dose (P=0.69).
        3. Nachshon (2018[7]) following 145 patients undergoing **peanut** OIT (age ≥ 4 years, median 5.8, interquartile range: 4.5-7, **88% were between 4 and 10** years old, 4.1% were >18 years old) observed that the 12 patients who failed desensitization were significantly younger than the 133 patients who were partially or fully desensitized (median 4.2 vs 6 yrs).

- A double-blind, placebo-controlled RCT included 169 **adolescents** (age 12 to 17) and 55 **adults** (age 18 to 55) with peanut allergy (Burks, 2018;[70] Vickery 2018[6]), with the percentage of adults who could tolerate ≥ 600 mg as a single dose being pre-specified as a secondary endpoint. There was no statistically significant difference between the OIT and the placebo groups in reaching this end-point.

Age range (years)	Proportion of patients who tolerated ≥ 600 mg peanut protein as a single dose: OIT versus placebo (n/N) – ITT analysis	Difference between OIT and placebo groups (95% CI)
4 to 11	70.6% (168/238) versus 4.5% (4/89)	66.1% (53.9 to 78.3), P<0.0001
12 to 17	**61.2% (82/134) versus 2.9% (1/35)**	**58.3% (39.7 to 76.9), P<0.0001**
18 to 55	**41.5% (17/41) versus 14.3% (2/14)**	**27.2% (-1.7 to 56.0), P=0.07**

- Double-blind, placebo-controlled RCT of **adolescents** with peanut allergy (mean age 15 years, range 12-18; age at diagnosis: 3 years) (Fauquert, 2018[55]): Peanut (or placebo) capsules were ingested daily over 24 weeks with increments every 2 weeks from 2 to 400 mg of peanut protein. ITT analysis: at DBPCFC, unresponsiveness to 400 mg of peanut protein was achieved in 81% (17/21) of OIT and 11% (1/9) of placebo patients (P<0.001, absolute difference = 0.7, 95%IC 0.43 0.96).
- Case series of 23 **adults** with OFC-confirmed IgE-mediated allergies who were treated with OIT (10 milk, 9 peanut, 4 egg) (Mantyla, 2018[71]): The median period of OIT was 515 days. The median dose of protein that could be tolerated increased from baseline 60-fold, 8-fold, and 35-fold in peanut, milk and egg-allergic subjects, respectively.

- **<u>Toddlers and pre-school children:</u>**
  - Vickery et al (2017[68]) randomized 37 children aged 9 to 36 months with OFC-confirmed peanut allergy to OIT with a maintenance dose of 300 or 3000 mg peanut protein per day. In the ITT analysis, 81% were desensitized to 20 peanuts (5000 mg peanut protein, OFC). Over a median of 29 months, an overall of 78% (29/37) children achieved a 4-week SU with 5000 mg of peanut protein (20 peanuts) (300 mg arm: 17/20 [85%]; 3000 mg, 12/17 [71%], P=0.43. Among 154 retrospectively identified matched control children who received standard care (avoidance), 6 demonstrated SU (3.9%), which was significantly lower than for the OIT group (P<0.001).
  - Martorell et al (2011[11]) randomized 60 children aged 24 to 36 months with OFC-confirmed milk allergy to OIT or avoidance. After one year, 90% (27/30) of OIT patients tolerated 200 mL milk compared to 23% (7/30) of control patients.
  - Soller et al 2019 (prospective multi-center study) reported that of 270 pre-school children (age 0.75-5.9 years, median 1.9 years) initiating peanut OIT, 243 (90%) reached the maintenance dose of 300-320 mg peanut protein (1.2-1.3 peanuts). [9] Of these, 87 patients had had a baseline reaction and an OFC after ~1 year of ingesting ~300mg peanut protein daily and 68 of them passed the OFC (78% = 68/87). For the 19 (21.9%) who reacted at the 1-year OFC, median cumulative dose increased from 12 mg (IQR: 10, 75) at baseline to 4000 mg (IQR: 4000 to 4000) at the 1-year OFC (change from baseline: 3988 mg [IQR: 3920, 3995]). (unpublished data on file from Canadian clinical practice)

Correlations between baseline parameters and OIT efficacy outcomes

Outcomes of RCTs with N≥ 50 that included children with a history of severe reactions:

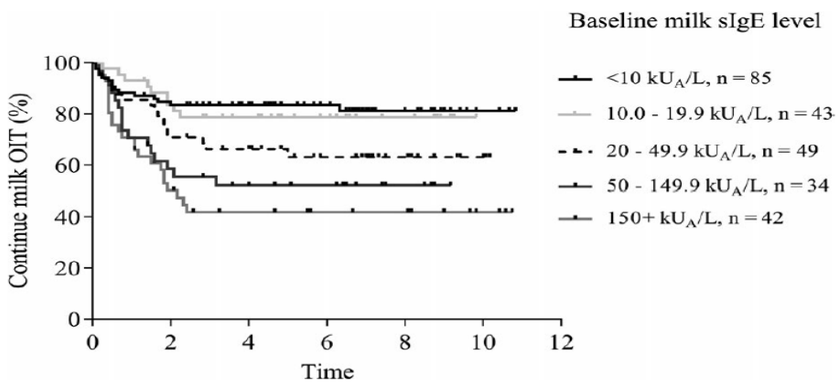
- **Anagnostou, 2014[1] (peanut** RCT, N=99, baseline worst clinical reaction WAO score grade 3 or 4: control 22.5% vs active 8.1%): **62%** (24/39; 95% CI 45–78) of patients were desensitized in the active group and none of the control group (0/46; 95% CI 0–9; P<0.001). 84% (95% CI 70–93) of the active group tolerated daily ingestion of 800 mg protein (5 peanuts). Median increase in peanut threshold after OIT was 1345 mg (range 45–1400; P<0.001) or 25.5 times (range 1.82–280; P<0.001).
- **Blumchen, 2019[2]** (**peanut**, N2=62: 31 OIT, 31 control): At baseline, 53% of children in the OIT group and 58% in the control group had a history of severe allergic reactions to peanut (grade IV or V[72]). The median sIgE was 81.5 kU/L (range 0.57-624 kU/L) and the median maximum tolerated single dose at the initial OFC was 30 mg peanut protein (range 1-3,000 mg). At the completion of the maintenance phase, 23/31 patients (**74%)** in the OIT group tolerated ≥ 300 mg peanut protein compared to 5/31 patients (**16%**) in the placebo group (P<.001); 13 (42%) patients in the OIT group tolerated 4.5 g peanut protein vs 1 patient (3.2%) in the placebo group (P<.001).
- **Longo, 2008[10]** (**milk** RCT, N=30 OIT, N=30 control): Included children with a baseline sIgE level > 85 kUA/L who had a positive history of at least one severe allergic reaction (defined as class 4 and 5 by Clark's classification) after accidental exposure to milk or dairy products requiring emergency treatment. After 1 year, 11/30 **(36%)** children receiving OIT achieved a daily intake of cow's milk of at least 150 mL, **54%** (16/30) were able to consume 5 to 150 mL of milk daily, and 10% (3/30) discontinued due to adverse reactions (respiratory or abdominal). No desensitization was observed in the control group.
- **Martin-Munoz, 2019a[20] (egg, RCT N=101 Age: 6-9 years):** Passing DBPCFC at 12 months with 3.3 g pasteurized raw egg white protein (cumulative) or reaching target dose of 3.3 g pasteurized raw egg white egg white protein (equivalent to 1 egg): OIT: **84%** (64/76) Control: **16%** (4/25)
- **Reier-Nilsen, 2019a[3]** (**peanut**, N=77: 57 OIT, 20 control): At baseline, 79% of children had a history of anaphylaxis to peanut and all children reacted with anaphylaxis during the baseline DBPCFC. At the end of the study, **21%** (12/57) of the OIT children reached the maintenance dose of 5000 mg peanut protein**, 54%** (31/57) reached a lower maintenance dose (250-4000 mg) and 25% (14/57) had discontinued. The only significant predictor of reaching a maintenance dose was the baseline peanut sIgG4/sIgE ratio (P=0.02).

Large case series

Baseline parameter	Outcome and correlation	Reference
History of anaphylactic reaction	Proportion (n/N) of patients with history of anaphylaxis (n) among all patients achieving the following outcomes (N): • Achieving the full target dose: 64% (102 [with history of anaphylaxis]/160 [all patients achieving this outcome]) • Achieving a partial dose: 91% (60/66) • Did not achieve any cow milk protein consumption: 82% (30/39) (P<0.001)	Levy, 2014[14] (milk, N=280)
	In multivariate analysis, history of anaphylaxis was **not** associated with reaching the maintenance dose.	Wasserman, 2019[8] (peanut, N=270)
Specific IgE serum levels	In logistic regression analysis, **treatment failure** (< 200 mL milk daily in long-term follow-up) was related to milk sIgE before OIT (P=0.000)	Kauppila, 2019[15] (milk, N=296)

	An increase of 1 KU/L in the pre-treatment peanut-specific IgE level led to a 2% decrease (P<.001) in the **likelihood of reaching the target dose**	Wasserman, 2019[8] (peanut, N=270)
Maximum tolerated dose of food allergen	Starting dose: median 120 mg cow milk protein; range (10-7200 mg). In multivariate logistic regression analysis, the most **important independent predictors for achieving the full dose included a maximal tolerated starting dose ≥ 30 mg of cow milk protein** (OR: 4.6, P<.001).	Levy, 2014[14] (milk, N=280)

Kauppila, 2019[15]



Wasserman, 2019[94]

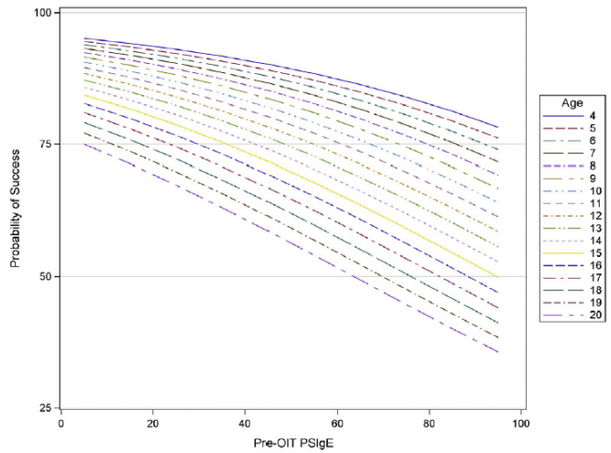


FIGURE 4. The probability of reaching the escalation target based on pretreatment PSIgE level and age at the start of therapy.

ADDITIONAL EVIDENCE - RCTs, CCTs and smaller case series

Baseline parameter	Outcome and correlation	Reference
History of anaphylactic reaction	History of anaphylaxis was **not** a potential predictor of food challenge results at 4 months.	Escudero, 2015[32] (RCT **egg**, N=30 OIT, N=31 control)
Specific IgE blood levels	In Tobit regression analysis, the baseline total IgE and the baseline sIgE were associated with the amount of peanut protein tolerated after OIT (P<0.001 for all).	Anagnostou, 2014[2] (RCT **peanut**, N=49 OIT, N=50 control)
	Desensitization was slower in patients with higher baseline sIgE levels: 9/10 (90%) patients in with sIgE <3.5 kU/L, 7/15 (50%) of patients with sIgE=3.5-17 kU/L, and 3/8 (30%) of patients with sIgE=17-50 kU/L achieved desensitization in < 3 months (P = 0.04).	Garcia-Ara, 2013[43] (CCT, **milk**, N=36 OIT; N=19 control)
Maximum tolerated dose of food allergen	In Tobit regression analysis, the amount of peanut protein tolerated at baseline was associated with the amount of peanut protein tolerated after OIT (P<0.001 for all).	Anagnostou, 2014[2] (RCT **peanut**, N=49 OIT, N=50 control)
	The dose that triggered symptoms at baseline was not a potential predictor of food challenge results at 4 months.	Escudero, 2015[32] (RCT **egg**, N=30 OIT, N=31 control)
	Baseline maximum dose allergen dose tolerated on the first day was not predictive of sustained unresponsiveness.	Burks, 2012[32] (RCT **egg**, N=40 OIT, N=15 control)

Correlations between baseline asthma status and OIT outcomes

Large case series

Outcome and correlation	Proportion of patients with asthma	Reference
Compared to patients without asthma (N=93), patients with asthma (N= 101) were **less likely to reach full desensitization** (7200 mg CMP) (52% vs 69%, P =.019). Among patients with asthma, need for controller therapy (initiated before or during OIT) was associated with lower likelihood of reaching full desensitization (P=0.001). Overall, 86% of all patients with asthma (87/101) and ≥ 82% of the sub-group requiring asthma controller therapy reached a dose likely protective against accidental exposure (>180 mg CMP).	101 patients with asthma, 93 no asthma	Elizur, 2015[73] (**milk**, N=194)
Baseline asthma was **not a statistically** significant predictor of treatment failure.	asthma: 73%	Kauppila, 2019[15] (**milk,** N=244)
History of asthma (intermittent, P=.291, or persistent, P = .170) was **not** a statistically significant predictor of reaching the target dose.	asthma: persistent: 43%, intermittent: 21%	Wasserman, 2018[8] (**peanut**, N=270)
Although more children with asthma (23%) vs without asthma (5.6%) had a single highest tolerated dose <5 mg peanut protein (P=.003), the two groups were **comparable in pre-OIT reaction severity and in the course and outcome of OIT**.	asthma: 56/145 [39%], controller therapy before OIT or initiated at the start of OIT: 34/145 [23%], uncontrolled asthma excluded	Nachshon, 2018,[7] (**peanut** , N=145)

Correlations between baseline multiple food allergies single-food OIT outcomes in large case series

Outcome and correlation	Reference
Percent of patients with other food allergies within the following outcome groups: • Achieved the full target dose: 18% • Achieved partial dose: 17% • Did not achieve any cow milk protein consumption: 13%, P=0.42	Levy, 2014[14] (**milk**, N=280)
Other food allergies: • Continued treatment: 49% (47/97) • Stopped treatment: 21% (3/14), P=0.08	Nachshon, 2018[7] (**peanut**, N=111)

CLINICAL SAFETY

Severe reactions /Systemic reactions/ anaphylaxis / serious adverse events / epinephrine use

Data for peanut, milk, egg allergies

Meta-analyses		
Nurmatov, 2017[29] – chicken's egg, cow's milk, peanut	**Romantsik, 2018[30] – chicken's egg**	**Chu, 2019[31] – peanut**
Absence of **systemic reactions** as assessed in 4 RCTs[34,36,38,42] and 1 CCT:[46] **-** milk/egg/peanut: 61%/21%/19% **OIT: 84%% (73/87)** **Control: 98% (62/63)** RR (C/OIT) = 1.16 (95% CI 1.03, 1.30) *Proportion of patients with systemic reactions:* *OIT: 16% (14/87)* *Control: 1.6% (1/63), P: significant*	Proportion of participants with **serious AEs (defined as ETR**) as assessed in 9 RCTs[18,19,32,34,35,37,51-53] and 1 CCT:[54] **OIT: 8.4% (21/249)** **Control: 0 (0/190)** RR= NA *GRADE assessment: low quality of evidence*	Proportion of participants with **ETRs** as assessed in 9 RCTs[1-6,42,55,66] **OIT: 12% (78/660)** **Control: 3.7% (12/324)** RR= 2.21 (1.27 to 3.83) *GRADE assessment (overall certainty of evidence): High* Proportion of participants with **anaphylaxis** as assessed in 9 RCTs[1,3-6,42,55,66] (1 unpublished): **OIT: 17% (108/653)** **Control: 2.6% (8/297)** RR=3.12 (95% CI 1.76, 5.55) *GRADE assessment (overall certainty of evidence): High* Proportion of participants with **serious AEs*** as assessed in 9 RCTs[1-6,42,55,66] (3 unpublished) **OIT: 6.2% (43/699)** **Control: 3.0% (10/338)** RR=1.92 (95% CI 1.00, 3.66) *GRADE assessment (overall certainty of evidence): Moderate* *Re-analysis to correct misclassification:* see section **8.2** **OIT: 21/699 (3.0%)** **Control: 11/338 (3.3%)**

ELORS: eosinophilic esophagitis-like oral immunotherapy- related syndrome; ETR: epinephrine-treated reaction; DBPCFC: double-blind placebo-controlled food challenge; RR: risk ratio (random effects model)
*Serious adverse events defined by US FDA as: causing death, a life-threatening state, hospitalization, disability, congenital abnormality, or an important medical event such as an urgent intervention to prevent the other outcomes) and if they caused treatment discontinuation

Case series with N> 150				
Levy, 2014[14] (Israel)– cow's milk **N=265** **Age: 4-27 (7.5 median) years** **Diagnosis confirmed with OFC: not for all patients**	**Kauppila, 2019[15] (Finland) – cow's milk** **N=295** **Age: 5-17 (median 7.5) years** **Diagnosis confirmed with OFC: yes**	**Soller, 2019[9] (Canada) – peanut** **N=270** **Age: 0.75-5.9 (median 1.9, IQR : 1.25-2.75) years** **Diagnosis confirmed with OFC: for 31% of patients**	**Wasserman, 2019[8] (USA) – peanut** **N=270** **Age: 4-18 (mean: 8.1) years** **Diagnosis confirmed with OFC: no**	**Wasserman, 2014[56] (USA and Israel)-peanut** **N=352** **Age: 3-24 years** **Diagnosis confirmed with OFC: 97% of patients**
Follow-up: ≥ 10 months after start of OIT **ETRs** during induction cycles (in clinic): **48%** (128/265) of patients **ETRs** during home-dosing phase: **17% (44/265**) of patients (58 ETRs per 77,098 doses= **0.08%**) % of ETRs at home= 58/186=**31%** **SEAs**: not reported	**Follow-up:** median 6.5 (range 1-11) years after start of OIT **Anaphylaxis** at least once after build-up phase: **14%** (34/237)- data missing from 59/295 patients **Possible SEAs**: One extremely severe anaphylaxis occurred in a patient after consumption of milk yogurt with a high concentration of cow's milk protein (8 g/100 mL), while he was on the aimed maintenance dose	**Follow-up:** median 20.0 weeks (build-up only) **Possible SAE:** **Grade 4 (severe symptoms)** (respiratory failure or hypotension or profound lethargy): **0.4%** (1/270) (1 per 2,321 doses administered in the office=0.04%) **ETR** during build-up phase: **4.1%** (11/270) of patients (12 ETRs per 41,020 doses = **0.029%** of doses with ETR) ETRs during in-office build-up: 6 per 2,321 doses = 0.26% ETRs during home dosing build-up: 6 per 38,699 doses = **0.016%** 50% of ETRs occurred at home 1.1% (3/270) of patients visited emergency departments for AEs, all of which were Grade 2. Grading according to Cox 2010[74] (modified)	**Follow-up**: ≥ 1 month after reaching maintenance and up to 8 years **ETRs** during build-up phase: **23%** (63/270) of patients (100 ETRs in total [37%] occurred in clinic) **SAEs**: 5 of 100 ETRs required 2 epinephrine doses and 2 required 3 doses; no ETR required > 3 epinephrine doses or intravenous fluids **ETRs** during maintenance phase: **13%** (28/214) of patients (63 ETRs in total, 40% occurred during the first 6 months) - sub-group: **patients treated for ≥ 3 years of maintenance**: **17%** (18/105) (43 ETRs) Incidence of ETRs during maintenance phase: 9.9/100 patient-years	**Follow-up**: from a few weeks to >7 after reaching maintenance **ETRs** during build-up phase: **10%** (36/352) of patients (57 ETRs per 79,726 doses = **0.07%** of doses with ETR - *corresponds to 26.1 ETRs per 100 patient-years, assuming 1 dose per day*) **ETRs** during maintenance phase: **6.4%** (19/298) of patients (38 ETRs per 160,265 doses, **0.02%** - *corresponds to 8.7 ETRs per 100 patient-years, assuming 1 dose per day*) Proportion of all ETRs that occurred in clinic: 29% (28/95) **Possible SAEs**: 3 patients received 2 doses of epinephrine for a single ETR; no patient required intravenous fluids for hypotension or other manifestations of shock.

RCTs with N>50 not included in meta-analyses

Martin-Munoz, 2019a[20] (Spain) – chicken's egg **N (OIT)=76 (88 including cross-over)** **Age: 6-9 years** **Diagnosis confirmed with OFC: yes**	**De Schryver, 2019[13] (Canada) – cow's milk** **N (OIT) = 26 (41 including cross-over), 26 control (4 of them withdrew)** **Age: 6-18, mean 12.1 years** **Diagnosis confirmed with OFC: yes (single-blind)**
Data from non-comparative phase: **ETRs during build-up phase:** **OIT: 8.0%** (7/88) of patients Control: NR **Grade 4 dosing adverse reactions** during build-up phase: **OIT: 9.2%** (7/76) of patients (15 DARs per 8448 doses, 0.2%) Control: NR **Grade 4 dosing adverse reactions** during maintenance phase: **OIT: 1.3%** (1/76) of patients (1 reaction) Control: NR No patient had moderate or severe adverse reactions because of egg consumption once they had finished the OIT. **Possible SAEs**: Build-up phase: No patient developed dysrhythmia and/or severe hypotension, hypovolemic shock, laryngeal edema, or respiratory or cardiac arrest Maintenance phase: One patient developed a grade 4 reaction after 2 months on maintenance after stopping OIT for 4 days due to intercurrent illness. Grading according to Sampson 2003[75]	*Data from comparative phase (first year of study):* **Anaphylactic** allergic reactions (multi-organ reaction or hypotension): **OIT (N=26)**: mean 5.5 reactions per patient **Control (N=22)**: 2 moderate reactions per 22 patients (mean 0.1 per patient) **ETRs:** **OIT (N=26)**: mean 0.5 per patient (SD 0.9) **Control (N=22)**: 2/22 patients (mean 0.1 per patient) *Data from non-comparative phase:* **Anaphylaxis**: OIT (N=41): Number of anaphylactic reactions per patient: mean 6.0 (245 reactions per 41 patients), median 4 (range 0-21, IQR 1-10, SD 3.5) **Severe anaphylactic reactions:** OIT (N=41): 2 severe anaphylactic reactions in 2 patients: 4.9% (2/41) of patients **ETRs:** OIT (N=41): mean 0.6 per patient (SD 1.2) Grading according to Muraro 2007[76]

Allergens other than milk, egg and peanut

	Nowak-Wegrzyn, 2019[24] (RCT, N=46) -wheat	**Kulmala, 2018[25] (case series, N=100) -wheat**	**Elizur, 2019[26] (CCT, N=73)-walnut**	**Barni, 2019 (case series, N=43) -hazelnut**	**Nachshon, 2019[28] (CCT) N=75 -sesame**
Age	Median, 8.7 years; range, 4.2-22.3	Mean 11.6 years, range, 6.1-18.6	Mean 7.9 years OIT, 6.8 years control; range 4-20	Mean 10 years, range: 5-16	Mean 7.5 years, ≥4, (IQR: 5.8-11.6)
Diagnosis	DBPCFC	Open OFC (not performed in 15 patients with an immediate reaction within the previous 3 months)	OFC, unless an immediate, recent (past year) reaction was documented	OFC	OFC or reaction within past year together with positive skin prick test (SPT) result and/or specific serum IgE (>0.35 kUA/L)
Adverse reactions	Among 7822 low-dose OIT doses in year 1, 15% were associated with	Allergic symptoms occurred in 94/100 children: mild in 34, moderate in 36	47/55 (85%) patients had an adverse reaction (mostly Grade 1 or 2) during	20/43 patients (46.5%) had no reactions and 23/43 patients had a	Build-up phase: Adverse reactions occurred in 127 of

	adverse reactions: 0.04% were severe, and 0.08% (were ETRs. Among 7921 placebo doses, 5.8% were associated with adverse reactions; none were severe. SAEs: Low-dose OIT: 2/23 (including 1 patient who was not randomized) Placebo: 5/23	and severe in 24 (24%). 12 patients (12%) had 13 ETRs % of patients with severe reactions by phase: Build-up (17 weeks – 3.3 months): 14% (14/100) Maintenance 1 (3 months): 7.8% (6/77) Maintenance 2 (9 months): 8.3% (6/72) Severe reactions were defined as objective respiratory symptoms, such as extensive coughing, inspiratory stridor or expiratory wheezing, and cardiovascular symptoms such as unconsciousness, lethargy, collapse, drop in blood pressure or tachycardia, alone or in combination with other symptoms. During the study, only bronchial wheezing, coughing, and laryngeal stridor occurred; no patient experienced a drop in blood pressure or cardiovascular collapse.	up-dosing in the clinic and 40 (73%) during the home-dosing phase The reactions were mostly mild (Grade 1 or 2) and occurred in response to 109 (4%) of the doses in clinic and 244 (2%) of home doses ETRs: 11 (20%) during the inhospital study phase and 8 patients had an ETR in response to a dose at home. During the maintenance phase, 1/45 patients had 1 ETR No severe reactions (≥ grade 3) were recorded during the study.	total of 55 reactions: 34 (61.8%) oral allergy syndrome, 8 (14.5%) rash, 6 (10.9%) abdominal pain, 2 (3.6%) urticaria, 2 (3.6%) angioedema, and 3 (5.4%) dyspnea	2,720 (4.7%) induction doses and 253 of 13,170 (2%) home doses ETR during the hospital build-up phase: 10 patients (16.7%) for 13/127 (9.4%) reactions ETR during home treatment: 5 patients (8.3%) for 7/ 253 (2.8%) reactions. No reactions worse than Grade I or II (WAO) occurred <u>Maintenance phase:</u> No ETR Grading according to Cox 2010[74] (modified)

ETR: epinephrine-treated reaction; DBPCFC: double-blind, placebo-controlled food challenge; SCD: successfully consumed dose; VWG: vital wheat gluten

Assessment of the quality of evidence

		Risk of bias (Cochrane tool[57] for interventional comparative studies; IHE tool[58] for case series)	**Level of evidence (Oxford Centre for Evidence-based medicine) -** adapted using the approach of the European Academy of Allergy and Clinical Immunology[59]
Peanut	**Interventional comparative studies (RCTs, CCTs):** meta-analysis (8 RCTs[1,2,4-6,42,55], 1 unpublished)	**Low**- 9 RCTs of which 8 rated as being at overall low risk of bias for ETRs and anaphylaxis	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: Soller, 2019[9], Wasserman, 2019,[8] Wasserman, 2014[56]	**Moderate** – 3 case series: 2 with retrospective study design	
Egg	**Interventional comparative studies (RCTs, CCTs):** Romantsik, 2018[30] (9 RCTs[18,19,32,34,35,37,51-53] and 1 CCT[54])	**High** – 10 RCTs of which all were rated as being at overall high risk of bias by ≥1 analysis	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series	**--**	
Milk/egg/ peanut	**Interventional comparative studies (RCTs, CCTs):** meta-analysis (4 RCTs[34,36,38,42] and 1 CCT)	**Moderate** – RCTs (3 low, 1 high risk of bias) and 1 CCT (moderate risk of bias)	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
Milk	**Interventional comparative studies (RCTs, CCTs):** 1 RCT (De Schryver, 2019[13])	**High** – unblinded, 4 control patients withdrew	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: Levy, 2014[14] and Kauppila, 2019[15] (clinical practice)	**Moderate** – 2 case series, main limit: retrospective study design	
Wheat	**Interventional comparative studies (RCTs, CCTs)**: Nowak-Wegrzyn, 2019[24]	**Low** – 1 RCT	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: 1 prospective case series in research context (Kulmala, 2018[25])	**Low** – 1 prospective case series	
Walnut	**Interventional comparative studies (RCTs, CCTs)**: Elizur, 2019[26] (CCT, N=73)	**High** – non-randomized control group,** unblinded	Level II (two groups, non-randomized studies)
	Case series: NA	**--**	
Hazelnut	**Interventional comparative studies (RCTs, CCTs)**:NA	**--**	Level II (two groups, non-randomized studies)
	Case series: Barni, 2019[27] (clinical practice)	**High** - 1 case series from clinical practice, limits: retrospective study design, single center, unclear recruitment and eligibility criteria	
Sesame	**Interventional comparative studies (RCTs, CCTs)**: Nachshon, 2019[28]	**High** – non-randomized control group,*** unblinded	Level II (two groups, non-randomized studies)
	Case series: NA	**--**	

Any adverse reactions / any allergic reactions / local reactions

Data for peanut, milk and egg allergy

Meta-analyses			RCT with N>50		Case series with N> 150		
Nurmatov, 2017[29] – chicken's egg and cow's milk	**Romantsik, 2018[30] – chicken's egg**	**Chu, 2019[31] – peanut**	**Martin-Munoz, 2019[20,21] – chicken's egg**	**De Schryver, 2019[13] (Canada) – cow's milk N (OIT) = 26 (41 including cross-over), 26 control (4 of them withdrew) Age: 6-18, mean 12.1 years Diagnosis confirmed with OFC: yes (single-blind)**	**Levy, 2014[14] (Israel)– cow's milk N=265 Age: 4-27 (7.5 median) years Diagnosis confirmed with OFC: not for all patients**	**Wasserman, 2019[8] (USA) – peanut N=270 Age: 4-18 (mean: 8.1) years Diagnosis confirmed with OFC: no**	**Soller, 2019[9] (Canada) – peanut N=270 Age: 0.75-5.9 (median 1.9, IQR : 1.25-2.75) years Diagnosis confirmed with OFC: for 31% of patients**
Absence of **local reactions** as assessed in 6 RCTs[11,12,32,34,37,38] and 1 CCT:[46] (Fig S21) - egg/milk: 61%/39% **OIT: 49% (89/183)** **Control: 98% (133/136)** RR (C/OIT) = 2.14 (95% CI 1.47, 3.12 *Proportion of patients <u>with</u> local reactions:* ***OIT: 51% (94/183)*** ***Control: 2.2% (3/136), P: significant***	Number of participants with **mild to severe AEs** as assessed in 9 RCTs[18,19,32,34,35,37,51-53] and 1 CCT:[54] **OIT: 75% (187/249)** **Control: 6.8% (13/190)** RR (OIT/C) = 8.35 (95% CI 5.31, 13.12) *GRADE assessment: low quality of evidence*	**Vomiting**[††] as assessed in 6 RCTs[2,4-6] (2 unpublished): **OIT: 39% (201/519)** **Control: 19% (44/236)** RR=1.79 (95% CI 1.35, 2.38) *GRADE assessment (overall certainty of evidence): High* **Angioedema**[‡‡] as assessed in 5 RCTs:[4-6] (2 unpublished) **OIT: 10% (51/489)** **Control: 3.9% (8/205)** RR=2.25 (95% CI 1.13, 4.47) *GRADE assessment (overall certainty of evidence): High* **Nasal congestion or blockage**,[§§] as assessed in 6 RCTs:[4-6,55] (2 unpublished) **OIT: 29% (149/510)** **Control: 18% (38/214)** RR=1.36 (95% CI 1.02, 1.81) *GRADE assessment (overall certainty of evidence): Moderate*	**Dose-adverse reactions (DARs):** **OIT: 87%** (66/76) **Control: 32%** (8/25) P<.001 DARs decreased in number and severity throughout the OIT and throughout the study (P < 0.05). **DARs during build-up phase:** **OIT: 91%** (67/76) of patients (420 DARs per 8448 doses, 4.9%) Control: NR **DARs during maintenance phase:** **OIT: 71%** (54/76) of patients (87 DARs) Control: NR	No comparative data for non-anaphylactic reactions	**Frequency of reactions during** home-dosing phase which were **not treated**: **OIT: 0.6%** (476 reactions per 77,098 doses) **Frequency of reactions during** home-dosing phase which were **treated with an antihistamine or a bronchodilator**: **OIT: 1.2%** (960 reactions per 77,098 doses)	Proportion of patients who reported **reactions that did <u>not</u> require epinephrine use**: **OIT: 58%** (157/270) patients (330 reactions)	≥ 1 allergic reaction during buildup phase: 68% (183/270) Grade 1 (mild) symptoms: 36% Grade 2 (moderate) symptoms: 31% Number of allergic reactions per patient: 1.99 (=538/270)

Meta-analyses			RCT with N>50		Case series with N> 150		
Nurmatov, 2017[29] – chicken's egg and cow's milk	**Romantsik, 2018[30] – chicken's egg**	**Chu, 2019[31] – peanut**	**Martin-Munoz, 2019[20,21] – chicken's egg**	**De Schryver, 2019[13] (Canada) – cow's milk N (OIT) = 26 (41 including cross-over), 26 control (4 of them withdrew) Age: 6-18, mean 12.1 years Diagnosis confirmed with OFC: yes (single-blind)**	**Levy, 2014[14] (Israel)– cow's milk N=265 Age: 4-27 (7.5 median) years Diagnosis confirmed with OFC: not for all patients**	**Wasserman, 2019[8] (USA) – peanut N=270 Age: 4-18 (mean: 8.1) years Diagnosis confirmed with OFC: no**	**Soller, 2019[9] (Canada) – peanut N=270 Age: 0.75-5.9 (median 1.9, IQR : 1.25-2.75) years Diagnosis confirmed with OFC: for 31% of patients**
		Any allergic/adverse reaction: 86% OIT (N=639) vs 61% control (N=278), RR=1.34 (1.12 to 1.60)					

††Similar findings for abdominal pain, mouth itching, and any allergic or adverse reaction. ‡‡Similar findings for urticaria. §§ Similar findings for asthma attack or wheeze

Allergens other than milk, egg and peanut

	Nowak-Wegrzyn, 2019[24] (RCT, N=46) -wheat	**Kulmala, 2018[25] (case series, N=100) -wheat**	**Elizur, 2019[26] (CCT, N=73)-walnut**	**Barni, 2019 (case series, N=43) -hazelnut**	**Nachshon, 2019[28] (CCT) N=75 -sesame**
Age	Median, 8.7 years; range, 4.2-22.3	Mean 11.6 years, range, 6.1-18.6	Mean 7.9 years OIT, 6.8 years control; range 4-20	Mean 10 years, range: 5-16	Mean 7.5 years, ≥4, (IQR: 5.8-11.6)
Diagnosis	DBPCFC	Open OFC (not performed in 15 patients with an immediate reaction within the previous 3 months)	OFC, unless an immediate, recent (past year) reaction was documented	OFC	OFC or reaction within past year together with positive skin prick test (SPT) result and/or specific serum IgE (>0.35 kUA/L)
Adverse reactions	Among 7822 low-dose OIT doses in year 1, 15% were associated with adverse reactions: 0.04% were severe, and 0.08% (were ETRs. Among 7921 placebo doses, 5.8% were associated with adverse reactions; none were severe. SAEs: Low-dose OIT: 2/23 (including 1 patient who was not randomized) Placebo: 5/23	Allergic symptoms occurred in 94/100 children: mild in 34, moderate in 36 and severe in 24 (24%). 12 patients (12%) had 13 ETRs % of patients with severe reactions by phase: Build-up: 14% (14/100) Maintenance 1 (3 months): 7.8% (6/77) Maintenance 2 (9 months): 8.3% (6/72)	47/55 (85%) patients had an adverse reaction (mostly grade 1 or 2) during up-dosing in the clinic and 40 (73%) during the home-dosing phase The reactions were mostly mild (grade 1 or 2) and occurred in response to 109 (4%) of the doses in clinic and 244 (2%) of home doses ETRs: 11 (20%) during the inhospital study phaseand 8 patients had an ETR in response to a dose at home. During the maintenance phase, 1/45	20/43 patients (46.5%) had no reactions and 23/43 patients had a total of 55 reactions: 34 (61.8%) oral allergy syndrome, 8 (14.5%) rash, 6 (10.9%) abdominal pain, 2 (3.6%) urticaria, 2 (3.6%) angioedema, and 3 (5.4%) dyspnea	<u>Build-up phase:</u> Adverse reactions occurred in 127 of 2,720 (4.7%) induction doses and 253 of 13,170 (2%) home doses ETR during the hospital build-up phase: 10 patients (16.7%) for 13/127 (9.4%) reactions ETR during home treatment: 5 patients (8.3%) for 7/ 253 (2.8%) reactions. No reactions worse than grade I or II

			patients had 1 ETR No severe reactions (≥ grade 3) were recorded during the study.		(WAO) occurred <u>Maintenance phase:</u> No ETR Grading according to Cox 2010[74] (modified)

ETR: epinephrine-treated reaction; DBPCFC: double-blind, placebo-controlled food challenge; SCD: successfully consumed dose; VWG: vital wheat gluten

Assessment of the quality of evidence

		Risk of bias (Cochrane tool[57] for interventional comparative studies; IHE tool[58] for case series)	**Level of evidence (Oxford Centre for Evidence-based medicine) -** adapted using the approach of the European Academy of Allergy and Clinical Immunology[59]
Peanut	**Interventional comparative studies (RCTs, CCTs):** meta-analysis (Chu, 2019[31])	**Low**	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: Soller, 2019[9], Wasserman, 2019[8]	**Low** – 2 case series, of which 1 had a low and the other a moderate risk of bias	
Egg	**Interventional comparative studies (RCTs, CCTs):** Romantsik, 2018[30] (9 RCTs[18,19,32,34,35,37,51-53] and 1 CCT[54]) plus 1 RCT (Martin-Munoz, 2019[20,21])	**High** —RCTs overall rated as being at high risk of bias	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series	**--**	
Egg / milk: 61%/39%	**Interventional comparative studies (RCTs, CCTs):** meta-analysis: 6 RCTs[11,12,32,34,37,38] and 1 CCT[46]	**Moderate** – of the 6 RCTs in the meta-analysis, 3 low, 2 high, and 1 unclear risk of bias) plus 1 CCT	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
Milk	**Interventional comparative studies (RCTs, CCTs):** NA	**--**	Level III: one group non-randomized
	Case series: Levy, 2014[14] (clinical practice)	**Moderate** – 1 case series, main limit: retrospective study design	
Wheat	**Interventional comparative studies (RCTs, CCTs)**: Nowak-Wegrzyn, 2019[24]	**Low** – 1 RCT	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: 1 prospective case series in research context (Kulmala, 2018[25])	**Low** – 1 prospective case series	
Walnut	**Interventional comparative studies (RCTs, CCTs)**: Elizur, 2019[26] (CCT, N=73)	**High** – non-randomized control group,** unblinded	Level II (two groups, non-randomized studies)
	Case series: NA	**--**	
Hazelnut	**Interventional comparative studies (RCTs, CCTs)**:NA	**--**	Level II (two groups, non-randomized studies)
	Case series: Barni, 2019[27] (clinical practice)	**High** - 1 case series from clinical practice, limits: retrospective study design, single center, unclear recrutement and eligibility criteria	
Sesame	**Interventional comparative studies (RCTs, CCTs)**: Nachshon, 2019[28]	**High** – non-randomized control group,*** unblinded	Level II (two groups, non-randomized studies)

	Case series: NA	--	

Discontinuations due to adverse events

Data for peanut, milk and egg allergy

Meta-analyses : Chu, 2019[31] – peanut	**RCT with N> 50 not included in meta-analysis**	**Case series with N> 150**		
		Levy, 2014[14] (Israel)– cow's milk N=280* Age: 4-27 (7.5 median) years Diagnosis confirmed with OFC: not for all patients	**Kauppila, 2019[15] (Finland) – cow's milk N=295 Age: 5-17 (median 7.5) years Diagnosis confirmed with OFC: yes**	**Wasserman, 2019[8] (USA) – peanut N=270 Age: 4-18 (mean: 8.1) years Diagnosis confirmed with OFC: no**
Discontinuations due to AEs as assessed in 9 RCTs[1-6,42,55,66] (3 unpublished): **OIT: 12% (87/699)** **Control: 2.4% (8/338)** RR=2.55 (95% CI 1.20, 5.42) *GRADE assessment (overall certainty of evidence): high*	Martin-Munoz, 2019[20,21] - **egg** Discontinuations due to AEs during build-up phase: **OIT: 18%** (16/88) Control: not reported Maintenance phase: not clear Burks, 2012[17] - **egg** : Before maintenance: **OIT: 13% (5/40)** (4 allergic reaction, 1 anxiety) **Placebo: 6.7% (1/15)** (1 allergy symptoms) During maintenance: **OIT: 2.9% (1/35)** (allergic reactions) (no maintenance for placebo) Overall: **15%** (6/40) Escudero, 2015[18] - **egg** **OIT: 6.7% (2/30)** (persistent mild reactions) **Control: 0/31** Fuentes-Aparicio, 2013[19] – **egg** : **OIT: 7.5% (3/40)** (persistent GI symptoms, including a case of confirmed EOE) **Control: 0/32** Morisset, 2007[12] – **milk** : **OIT : 7.1% (2/28)** **Control : 0/32**	**Follow-up:** ≥ 10 months after start of OIT **Total discontinuations due to AEs or treatment failure: 9.6%** (27/280): **Primary failures (stopped OIT during the 1st week): 1.8%** (5/280) (3 extreme sensitivity, 2 parental or psychological reasons-not AE) **Recurrent anaphylaxis: 5.7%** (16/280, 59% [16/27 of all] **GI symptoms with peripheral blood eosinophilia: 2.9%** (8/280) **Food aversion: 3.6%** (10/280, percent of patients who discontinued after 1st week: 45% [10/22]) **Total discontinuations: 14%** (39/280)	**Follow-up:** median 6.5 (range 1-11) years after start of OIT Over median FU of 6.5 years 24% (71/295) of patients discontinued OIT (data missing from 15% [44/295] of patients) **GI symptoms** were the most common self-reported reason for discontinuation: **16%** (41/252), **58%** (41 of 71 discontinuations) Other reasons: cutaneous (34/71, 48%), respiratory (24/71, 34%), anaphylaxis (22/71, 31% - **7.5% of 295**), oropharyngeal (21/71, 30%), food aversion (7/71, 10%), ocular (5/71, 7%), lack of progress (4/71, 6%), and miscellaneous (8/71, 11%).	**Follow-up**: ≥ 1 month after reaching maintenance and up to 8 years Build-up phase **Loss to FU:** 2.0% (6/270) **Discontinuations, total**: 16% (42/270) **ETR: 3.0%** (8/270, 19% of discontinuations) **ELORS: 7.8%** (21/270, 50% of discontinuations) **Other AEs: 1.9%** (5/270, 12% of discontinuations) **Total discontinuations due to AEs: 13%** (34/270, 81% of discontinuations) **Food aversion: 0.7%** (2/270, 4.8% of discontinuations) **Other** (anxiety, burden of care, perception, sibling with OIT): **2.2%** (6/270, 14% of discontinuations) Maintenance phase **Loss to FU:** 15% (33/214) **Discontinuations, total**: **12%** (25/214) of patients (- sub-group: patients treated for ≥ 3 years of maintenance: 11% [12/105]) **ETR: 1.4%** (3/214, 12% of discontinuations) **ELORS: 0.5%** (1/214, 4.0% of discontinuations) **Other AEs: 1.9%** (4/214, 16% of discontinuations)

Meta-analyses : Chu, 2019[31] – peanut	RCT with N> 50 not included in meta-analysis	Case series with N> 150		
		Levy, 2014[14] (Israel)– cow's milk N=280* Age: 4-27 (7.5 median) years Diagnosis confirmed with OFC: not for all patients	**Kauppila, 2019[15] (Finland) – cow's milk N=295 Age: 5-17 (median 7.5) years Diagnosis confirmed with OFC: yes**	**Wasserman, 2019[8] (USA) – peanut N=270 Age: 4-18 (mean: 8.1) years Diagnosis confirmed with OFC: no**
				Total discontinuations due to AEs: 3.7% (8/214, 32% of discontinuations) **Food aversion: 5.1%** (11/214, 44% of discontinuations) **Other** (perception, irregular dosing, failed SU): **2.8%** (6/214, 24% of discontinuations) **Incidence of discontinuations:** 3.9/100 patient-years **Discontinuations due to AEs in b**oth phases combined: 42/270=**17.5%**

* At date of data cut-off, 15 patients continued to receive increasing amounts of cow milk (i.e., have not completed the build-up phase).

Allergens other than milk, egg and peanut

	Nowak-Wegrzyn, 2019[24] (RCT, N=46) -wheat	**Kulmala, 2018[25] (case series, N=100) -wheat**	**Elizur, 2019[26] (CCT, N=73)-walnut**	**Barni, 2019 (case series, N=43) -hazelnut**	**Nachshon, 2019[28] (CCT) N=75 -sesame**
Age	Median, 8.7 years; range, 4.2-22.3	Mean 11.6 years, range, 6.1-18.6	Mean 7.9 years OIT, 6.8 years control; range 4-20	Mean 10 years, range: 5-16	OFC or reaction within past year together with positive skin prick test (SPT) result and/or specific serum IgE (>0.35 kUA/L)
Discontinuations	11/46 (24%) subjects discontinued the study: 1 subject in the low-dose VWG OIT group discontinued after completing the year 2 OFC, 6 subjects discontinued the study before week 52 and were counted as failures for the primary end point; 4 in the active VWG OIT arm (3 because of dosing-	Total: 43% (43/100) Build-up: 23/100 (23%) – dropouts due to severe reaction: 7.0% (7/100) (14 had severe reaction) Maintenance phase 1 (3 months): 6.5% (5/77) – dropouts due to severe reaction: 1/77 (1.3%) (6 had severe reaction) Follow-up (maintenance phase 2: 9 months): 21% (15/72) – dropouts due	one patient of those who had an ETR discontinued 1.8% (1/55)	Not reported	<u>Build-up phase:</u> No discontinuation <u>Maintenance phase:</u> No discontinuation due to AEs (2 discontinued because of treatment burden, 2 because of food aversion)

	related symptoms and 1 because of participant's decision) and 2 in the placebo arm (1 because of participant's decision and 1 because of nonadherence). In addition, in the high-dose crossover group 2 subjects discontinued participation because of dosing symptoms (1 was given a diagnosis of both ulcerative colitis and EoE) and 1 because of nonadherence. Discontinuation due to AEs in low-dose VWG during the build-up phase: 3/23 (13%) OIT vs 0 placebo In maintenance phase: 1/19 (5.3%)	to severe reaction: 1/72 (1.4%) (6 had severe reaction) Combining both maintenance phases: 26% (20/77) – dropouts due to severe reaction: 2/77 (2.6%) (6 had severe reaction) 34/ 43 (79%) had objective or objective and subjective symptoms and 8/43 (16%) only had subjective symptoms			

ETR: epinephrine-treated reaction; DBPCFC: double-blind, placebo-controlled food challenge; SCD: successfully consumed dose; VWG: vital wheat gluten

Assessment of the quality of evidence

		Risk of bias (Cochrane tool[57] for interventional comparative studies; IHE tool[58] for case series)	**Level of evidence (Oxford Centre for Evidence-based medicine) -** adapted using the approach of the European Academy of Allergy and Clinical Immunology[59]
Peanut	**Interventional comparative studies (RCTs, CCTs):** meta-analysis (Chu, 2019[31])	**Low**	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: Wasserman, 2019[8]	**Moderate** – 1 case series, main limit: retrospective study design	
Egg	**Interventional comparative studies (RCTs, CCTs):** Burks, 2012[17], Escudero, 2015[18] Fuentes-Aparicio, 2013[19]	**Moderate** – 3 RCTs: 1 low, 1 high, 1 unclear risk of bias	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series	**--**	
Milk	**Interventional comparative studies (RCTs, CCTs):** Morisset, 2007[12]	**High** – 1 RCT at high risk of bias	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: Levy, 2014[14] (clinical practice)	**Moderate** – 1 case series, main limit: retrospective study design	
Wheat	**Interventional comparative studies (RCTs, CCTs)**: Nowak-Wegrzyn, 2019[24]	**Low** – 1 RCT	Level I (Systematic reviews, meta-analysis, randomized controlled trials)
	Case series: 1 prospective case series in research context (Kulmala, 2018[25])	**Low** – 1 prospective case series	
Walnut	**Interventional comparative studies (RCTs, CCTs)**: Elizur, 2019[26] (CCT, N=73)	**High** – non-randomized control group,** unblinded	Level II (two groups, non-randomized studies)
	Case series: NA	**--**	

Hazelnut	**Interventional comparative studies (RCTs, CCTs)**:NA	**--**	--
	Case series: NA	**--**	
Sesame	**Interventional comparative studies (RCTs, CCTs)**: Nachshon, 2019[28]	**High** – non-randomized control group,*** unblinded	Level II (two groups, non-randomized studies)
	Case series: NA	**--**	

Long-term FU for safety and tolerability

LTFU of RCTs (with control arm)			Large observational studies (case series)			
Jones, 2016[60] – LTFU of Burks, 2012 (egg)[32] Diagnosis confirmed with OFC: no	**Hsiao, 2017[61] – LTFU of Tang 2015 (peanut):[4]** Diagnosis confirmed with OFC: no	**Meglio, 2017[62] – LTFU of Meglio 2013 (egg)[37]** Diagnosis confirmed with OFC: yes (DBPCFC)	**Manabe, 2019[77] (Japan)* - egg, cow's milk, or wheat** N=130 Age: 6-NR (children) Diagnosis confirmed with OFC: yes (DBPCFC)	**Kauppila, 2019[15] (Finland) – cow's milk** N=295 Age: 5-17 (median 7.5) years Diagnosis confirmed with OFC: yes	**Elizur, 2016[16] (Israel) - cow's milk** N=196 Age: >6, mean 10 years Diagnosis confirmed with OFC: yes, for patients who did not have an anaphylactic reaction in the preceding year	**Nachshon, 2018[7] (Israel)- peanut** N=145 Age: ≥4 (median 5.8) years Diagnosis confirmed with OFC: yes, for patients who did not have an anaphylactic reaction in the preceding year
Patients followed: All patients who started OIT or control therapy **Follow-up**: Point 1: approx. 5 years after study enrolment; Point 2: 1 year later **Completeness of follow-up**: OIT: 85% (34/40); placebo: 73% (11/15) at both time points Year 3 and 4 after initiation of OIT: 3 egg-related reactions, 2 in OIT-desensitized subjects including **1 ETR in a patient who had achieved SU** 19.4 months prior and reported unrestricted egg consumption.	**Patients followed:** All patients who started OIT or control therapy **Follow-up:** Mean of 4.2 years (SD 0. 7) from treatment cessation **Completeness of follow-up**: 77% (OIT: 24/31; placebo: 24/71) of patients **No ETR, no anaphylaxis** **Estimated number of reactions per 10 person-years:** OIT: 1.1 (99.9 person-year of FU) Placebo: 0.9 (102 person-years of FU)	**Patients followed:** All patients who started OIT or control therapy **Follow-up:** Mean of 2.5 (SD 0.3) and 7 (SD 0.9) years after original study start **Completeness of follow-up**: 2.5-year follow up: 19/20; 7-year follow-up: 18/20 **No ETR, no need for emergency care**	**Patients followed:** Patients who achieved a 2-week SU within 2 years after starting OIT **Follow-up:** ≥ 1 year (median 3.6) since achieving a 2-week SU **Completeness of follow-up**: 85% (108/130) <u>Adverse reactions in follow-up period among patients with follow-up:</u> **Any medication-treated symptoms**: 44/108 (41%) - Egg: 17/61 (28%); Cow's milk: 17/30 (57%); Wheat: 10/17 (59%) **Any moderate or severe medication-treated symptoms**: 24/108 (22%) **ETRs**: 2 (1 egg, 1 wheat)/108 (1.9%)	**Patients followed:** All patients who started OIT **Follow-up**: median 6.5 years (range 1-11) **Completeness of follow-up**: 83% (244/295) of patients <u>ETRs in the past year among the patients with follow-up</u>: Patients consuming ≥200 mL/d milk: 1.6% (2/122) Patients consuming <200 mL/d milk: 5.6% (2/36) *Patients consuming any milk: 2.5% (4/158)* Patients avoiding milk: 8.9% (4/45) P=0.09 <u>Any milk-related side-effect in the past year among the patients with follow-up</u>: Patients consuming ≥200 mL/d milk: 37% (45/122)	**Patients followed:** Patients who reached full cow milk protein consumption **Follow-up**: ≥ 6 months after completing up-dosing phase; median: 24.8 (range 6–41) months **Completeness of follow-up**: 195/196 (99%) of patients <u>Adverse reactions during follow-up period</u>**:** **ETRs**: 13/195 (6.7%) **Any AE** due to cow milk: 100/195 patients (51%) Respiratory: 57/195 (29%) GI: 17/195 (8.7%) **Rate of AEs following completion of up-dosing:** Month 6–15 months (n=29): 0.28/month Month 15–30 months (n=39): 0.21/month	**Patients followed:** All patients who started OIT **Follow-up:** ≥ 6 months after completing build-up phase; median: 18 (range 6–75) months **Completeness of follow-up**: 142/145 (98%) of all patients 130/133 (98%) of patients reaching 3000 mg (n=113) or 300-2400 mg (n=20) PP at end of up-dosing <u>Adverse reactions during follow-up period among patients consuming 300-3000 mg PP</u> : **ETRs:** 2/130 (1.5%) **Any objective reaction**: 12/130 (9.2%)

			73% (32/44) patients reporting symptoms attributed their symptoms to co-factors such as exercise, fatigue or illness 59% (22/ 37) of patients with clear responses) experienced their first symptoms ≥2 years after 2-week SU	Patients consuming <200 mL/d milk: 81% (29/36) *Patients consuming any milk: 47% (74/158)* Patients avoiding milk: 67% (30/45) P=0.000 Among patients who consumed ≥200 mL/d milk, those with longer follow-up tended to have fewer side effects (P = 0.07)	After > 30 months (n=28): 0.15/month P < .01	

*Included for this outcome event though N<150 for each allergen because of scarcity of long-term data after SU

ASSESSMENT OF THE QUALITY OF EVIDENCE

		Risk of bias (Cochrane tool[57] for interventional comparative studies; IHE tool[58] for case series)	**Level of evidence (Oxford Centre for Evidence-based medicine) -** adapted using the approach of the European Academy of Allergy and Clinical Immunology[59]
Peanut	**Interventional comparative studies (RCTs, CCTs):** Hsiao, 2017[61]	**High**- 1 LTFU on RCT, limitations: open-label and loss to follow-up	Level II two groups, non-randomized studies
	Case series: Nachshon, 2018[7]	**Moderate** – 1 case series, main limit: retrospective study design, single center	
Egg	**Interventional comparative studies (RCTs, CCTs):** Jones, 2016[60], Meglio, 2017[62]	**High** – 2 LTFU on RCTs, limitations: open-label and loss to follow-up	Level II two groups, non-randomized studies
	Case series	**--**	
Milk	**Interventional comparative studies (RCTs, CCTs):**	**--**	Level III: one group non-randomized
	Case series: Kauppila, 2019[15], Elizur, 2016[16], Manabe, 2019[77]	**Moderate** – 3 case series, main limit: retrospective study designs, single center	
Wheat	**Interventional comparative studies (RCTs, CCTs)**: NA	**--**	Level III: one group non-randomized
	Case series: Manabe, 2019[77]	**Moderate** – 1 case series, main limit: retrospective study designs, single center	
Walnut	**Interventional comparative studies (RCTs, CCTs)**: NA	**--**	--
	Case series: NA	**--**	
Hazelnut	**Interventional comparative studies (RCTs, CCTs)**:NA	**--**	--
	Case series: NA	**--**	
Sesame	**Interventional comparative studies (RCTs, CCTs)**: NA	**--**	--
	Case series: NA	**--**	

Eosinophilic esophagitis

Meta-analyses		Large case series (N> 150)			
Chu, 2019[31] – peanut	**Lucendo, 2014[78] – chicken's egg, cow's milk, peanut and others**	**Goldberg, 2017[79] (Israel) - milk, peanut, egg, sesame** N=794 Age: median 83 months (IQR 60-126) Diagnosis confirmed with OFC: yes, for patients who did not have an anaphylactic reaction in the preceding year	**Wasserman, 2019[8] (USA) – peanut** **N=270** **Age: 4-18 (mean: 8.1) years** **Diagnosis confirmed with OFC: no**	**Kauppila, 2019[15] (Finland) – cow's milk** **N=295** **Age: 5-17 (median 7.5) years** **Diagnosis confirmed with OFC: yes:**	**Soller, 2019[9] (Canada) – peanut** **N=270** **Age: 0.75-5.9 (median 1.9, IQR : 1.25-2.75) years** **Diagnosis confirmed with OFC: for 31% of patients**
3 events of EOE occurred in 3 RCTs; another 2 RCTs reported explicitly that no EOE occurred (N=719), all in the OIT group – *no statistical analysis performed*	Meta-analysis of 9 studies (8 retrospective case series, 1 RCT, published up to March 2014) that reported on a total of 708 patients receiving OIT (including baked milk introduction), indicated that 2.7% of patients undergoing OIT newly developed EOE (95% CI 1.7% to 4.0%).	**Recurrent GI symptoms (abdominal pain and/or vomiting) independent of the timing to dose administration:** 8.2% (65/794) Milk: 9.0% (55/614) Peanut: 6.9% (9/130) Egg: 2.4% (1/41) 39% (25/65) of cases occurred within the first month and 86% (56/65) within the first 3 months of OIT 69% (45/65) resumed OIT and 42 did not redevelop symptoms* No dysphagia, no food impaction. 3 patients underwent biopsy showing increased esophageal eosinophilic counts In all cases in which the dosage was reduced or stopped, symptoms subsided, and peripheral eosinophil counts decreased. Patients with recurrent GI symptoms had higher peripheral eosinophil counts at baseline (P=0.046) and higher increases in peripheral eosinophil counts during OIT (P<0.001) compared to other patients, but did not differ in age and sex.	**ELORS:** EOE-like OIT-related syndrome: episodic vomiting occurring > 2 hours after dosing <u>Build-up phase:</u> Proportion of patients with **ELORS**: **14%** (**37**/270) (documented increase in peripheral blood eosinophils: 4.8% (13/270), only 16 of 37 tested) Biopsies were performed in 2/37 patients (results not reported); 18/37 patients were treated with a PPI for 1-4 weeks and 1/37 with an oral corticosteroid for < 14 days Proportion of patients with ELORS who: -discontinued: 57% (21/37) -reached target maintenance dose: 35% (13/37) -Discontinued for other reasons or transferred care: 8.1% (3/37) None of the 35 patients with ELORS with follow-up (2 transferred care) had persistent symptoms or required prolonged therapy. <u>Maintenance phase:</u> Proportion of patients with **ELORS** during maintenance phase: **0.5%** (1/214) – discontinued OIT	One patient with vomiting and failure to thrive underwent endoscopy, which was negative for EOE; the examination was performed after OIT discontinuation while the patient was on a milk-avoidance diet.	1.1% (3/270) of patients experienced symptoms suggestive of EoE, 1 biopsy performed (no EoE) An additional case of EoE identified incidentally during a biopsy to rule out celiac disease (the EoE persisted despite stopping OIT)

			Incidence of **ELORs** during maintenance phase: 0.16/100 patient-years		

* Goldberg (2019[80]) reported details on the management and the treatment course of these patients: the cumulative daily dose was reduced by a median of 50% in 66% (43/65) of patients, dose increases were deferred in 3.1% (2/65) of patients, or treatment was temporarily suspended in 28% (18/65) of patients. Symptoms and eosinophilia abated on dose modification, allowing for resumption of dose increases for 34 patients or reinitiation of treatment for 9 patients. OITIGER reoccurred 18.5% (10/54) of patients and resolved after further dose modification. In long-term follow-up (>3-26 months), patients with OITIGER had a higher OIT failure rate (P=.004) and were less likely to reach full desensitization (P < .001).

Smaller case series	
Echeverria-Zudaire, 2016[81] (Spain) - milk (N=97) or egg (31) **N=128** **Age: children** **Diagnosis confirmed with OFC: yes (open)**	**Gomez Torrijos, 2017[82] and Rodriguez, 2014[83] (Spain) – milk** **N=57** **Age: children** **Diagnosis confirmed with OFC: NR**
Biopsy-confirmed EOE: 6.3% (8/128) 6 patients developed EOE at a median of 29 months (range 15-48) after OIT(all with cow's milk); 2 developed EOE during OIT (egg and milk plus egg) Most of the 8 patients were males between 3 and 14 years of age. **EOE with oesophageal involvement only**: 4.5% (6/128) 5/6 continued OIT with PPI (n=3) or PPI plus fluticasone (n=2); 4/5 underwent follow-up endoscopy: 3 histological remission, 1 continued EOE. Histological remission was confirmed in the patient who discontinued OIT. **EOE - plus duodenal or colon involvement**: 1.6% (2/128) Both discontinued OIT and underwent follow-up endoscopy which showed histological remission in both cases	**Biopsy-confirmed EOE: 5.3% (3/57**) of patients treated with OIT for cow milk allergy All three patients were males and developed symptoms (including dysphagia) after reaching complete desensitization and/or while on maintenance. All patients discontinued milk intake, redeveloped sensitization and started avoiding milk. Biopsies performed 6-24 months after starting avoidance showed resolution of EOE.

Impact of patient characteristics on safety outcomes

- Most OIT studies enrolled children and adolescents starting from age 4 to 7 years, with median/mean ages in the range of 6 to 12 years (Anagnostou, 2014;[1] Bird, 2018;[5] Burks, 2012;[32] Elizur, 2016;[16] Escudero,2015;[18] Fuentes-Aparicio, 2013;[19] Kauppila, 2019;[15] Levy, 2014;[14] Longo, 2008;[10] Martin-Munoz, 2019;[20] Nachshon, 2018;[7] Reier-Nilsen, 2019;[3] Vickery, 2018[6] and Wasserman, 2019[8]). Three studies enrolled peanut-allergic children starting from a younger age, three years (Blumchen, 2019;[2] Wasserman, 2014[56]) or one year (Tang, 2015[4]). One study enrolled children for milk or egg OIT starting from the age of one year (Morisset, 2007[12]).

- **Older children, adolescents and adults**

  - No association between baseline age and safety outcomes in large case series of children and adolescents (N 130 to 295) (Wasserman 2019[8], Elizur, 2016;[16] Kauppila, 2019;[15] Levy 2014[14])

  - A double-blind, placebo-controlled RCT included 55 adults (18 to 55) and 169 adolescents (age 12 to 17) with peanut allergy (Burks, 2018;[70] Vickery 2018[6]). There was no apparent difference between age groups in the proportion of patients with treatment-emergent hypersensitivity adverse events.

Age range (years)	N (OIT)	N (placebo)	Proportion of patients experiencing event OIT versus placebo			
			Treatment-emergent allergic hypersensitivity adverse events	Severe adverse event	Serious adverse events	Anaphylaxis/Systemic allergic reaction
4 to 11	238	89	86.1% versus 69.7%	4.3% vs 0.8%	2.4% vs 0.8%	14.2% vs 3.2%
12 to 17	**134**	**35**	**89.6% versus 68.6%**			
18 to 55	**41**	**14**	**87.8% versus 78.6%**	**4.9% vs 7.1%**	**4.9% vs 7.1%**	**19.5% vs 7.1%**

  - Double-blind, placebo-controlled RCT of adolescents with peanut allergy (mean age 15 years, range 12-18; age at diagnosis: 3 years) (Fauquert, 2018[55]): Peanut (or placebo) capsules were ingested daily over 24 weeks with increments every 2 weeks from 2 to 400 mg of peanut protein. **Five severe multi-system reactions (grades 3a and 3b) occurred in 4 OIT patients (19%= 4/21) and in none (0) in the placebo group.**

  - Case series of 23 adults with OFC-confirmed IgE-mediated allergies who were treated with OIT (10 milk, 9 peanut, 4 egg) (Mantyla, 2018[71]): The median period of OIT was 515 days. **ETRs: 17% (4/23); emergency room treatments: 13% (3/23).**

- **Toddlers and pre-school children:**

  - Vickery et al (2017[68]) randomized 37 preschool children aged 9 to 36 months with OFC-confirmed peanut allergy to OIT with a maintenance dose of 300 or 3000 mg peanut protein per day. One ETR occurred in the high dose group (5.9%, 1/17) and none in the low-dose group. **There were no treatment-related severe adverse events.**

  - Martorell et al (2011[11]) randomized 60 children aged 24 to 36 months with OFC-confirmed milk allergy to OIT or avoidance. **Two ETRs occurred in 2 children in the OIT group (6.7%, 2/30); no severe reactions occurred.**

  - Soller et al (2019,[9] prospective multi-center study) reported that of 270 pre-school children (age 0.75-5.9 years, median 1.9 years) undergoing peanut OIT 36% (98/270) experienced grade 1 (mild) symptoms, 31% (84/270) grade 2 (moderate), and 0.4% (1/270) grade 4 (severe) symptoms graded according to the World Allergy Organization Subcutaneous

Immunotherapy Systemic Reaction Grading System[74]). Eleven patients (4.1%, 11/270) experienced a total of 12 ETRs during build-up (11 for grade 2 reactions and 1 for a grade 4 reaction). Half of the ETRs (6) occurred in the clinic during up-dosing and the other half at home. Overall, a total of 0.029% of doses during build-up were associated with an ETR.

Impact of baseline food allergy-related parameters on safety outcomes

Inclusion of patients with a history of severe reactions in OIT studies:

- Among 13 RCTs with N> 50, 6 excluded patients with a history of severe anaphylaxis (Burks, 2012;[32] Escudero, 2015;[32] Martorell, 2011;[32] Tang, 2015;[4] Bird, 2018;[5] Vickery; 2018;[6] Sampson, 2019[63]), which was commonly defined as hypotension, neurological and/or respiratory compromise. Other RCTs (Longo, 2008,[10] Martin-Munoz, 2019a,[20] Reier-Nilsen, 2019a[3]) either did not list anaphylaxis among their exclusion criteria or, additionally, specifically stated that they did not exclude children with a history of severe allergic reactions (Blumchen, 2019;[2] Anagnostou, 2014[2]). (For another 2 studies [Fuentes-Aparicio, 2013, Morisset, 2007], inclusion of patients with severe anaphylaxis was not clear.
    - In peanut RCTs, inclusion criteria for the minimum serum peanut-specific IgE level ranged from 0.35 to15 kU/L; there was no maximum sIgE level specified (Chu, 2019).[31]
- Large case series (clinical practice) generally did not exclude patients with a history of anaphylaxis; two of them explicitly state that no patient was excluded because of the severity of their previous reactions or their sIgE levels (Wasserman, 2018;[94] Wasserman, 2014[56]).

Outcomes of RCTs with N≥ 50 that included children with a history of severe reactions:

- **Anagnostou, 2014[2]** (**peanut** RCT, N=99, baseline worst clinical reaction WAO score grade 3 or 4: control 22.5% vs active 8.1%): ETRs occurred after 0.01% of doses (1 participant); OIT vs placebo: 2.0% (1/49) vs 9 (0/50). There were no SAEs.
- **Blumchen, 2019[2]** (**peanut** RCT, N2=62: 31 OIT, 31 control): At baseline, 53% of children in the OIT group and 58% in the control group had a history of severe allergic reactions to peanut (grade IV or V[72]). The median sIgE was 81.5 kU/L (range 0.57-624 kU/L) and the median maximum tolerated single dose at the initial OFC was 30 mg peanut protein (range 1-3,000 mg). Wheezing was the only objective symptom reported significantly more often in the OIT group (8 events in 6 patients) than in the placebo group (1 patient; P=.045). There were no ETRs; the rate of serious AEs was 10% (3/30) in the OIT group and 16% (5/31) in the placebo group.
- **Longo, 2008[10]** (**milk** RCT, N=30 OIT, N=30 control): Included children with a baseline sIgE level > 85 kUA/L who had a positive history of at least one severe allergic reaction (defined as class 4 and 5 by Clark's classification) after accidental exposure to milk or dairy products requiring emergency treatment. In the OIT group, almost all patients had allergic reactions; 4 ETRs occurred in 4 OIT patients (13%) during the initial hospital-based rush phase and 1 ETR (3.3%) during the home dosing phase. During the home dosing phase, 2/30 (6.7%) children attended the emergency department. In the control group, 6/30 (20%) children had mild adverse reactions caused by accidental exposure to milk.
- **Martin-Munoz, 2019a[20] (egg,** RCT**):** (N=88 OIT, 25 controls) ETRs: 8.0% OIT vs Control: NR; No SAEs
- **Reier-Nilsen, 2019a[3]** (**peanut**, N=77: 57 OIT, 20 control): At baseline, 79% of children had a history of anaphylaxis to peanut and all children reacted with anaphylaxis during the baseline DBPCFC. During up-dosing, 11/57 (19%) of children in the OIT group experienced 11 anaphylaxis events (classified as moderate), including 6 ETRs; the control group did not experience any anaphylactic reactions to peanut.

Correlations between baseline parameters and OIT safety and tolerability outcomes

LARGE CASE SERIES

Baseline parameter	Outcome and correlation	Reference
History of anaphylactic reaction	Associated with **adverse reactions** after the completion of treatment (median follow-up 24.8, range 6-41) months after completion of the build-up phase (OR=2.1, P=.033)	Elizur, 2016[16] (milk, N=197)
	History of anaphylaxis among the following sub-groups by outcome: • Continued treatment: 39% (38/97) • Stopped treatment: 71% (10/14), P=0.04	Nachshon, 2018[7] (peanut, N=111)
	In multivariate analysis, history of anaphylaxis was **not** associated with ELORS or ETRs	Wasserman, 2018[94] (peanut, N=270)
Specific IgE serum levels	In logistic regression analysis, milk-related anaphylaxis after buildup was related to milk sIgE before OIT; for every additional sIgE doubling, the **risk of anaphylaxis** increased by 60% (OR 1.6) (P=0.000)	Kauppila, 2019[15] (milk, N=296)
	Higher sIgE increased the risk of **ELORS** (P <.001) and of **ETRs** (P=0.19) occurring during escalation	Wasserman, 2018 (peanut, N=270)
	In a multivariable logistic regression model those with a higher baseline IgE were more likely to **drop out** during P-OIT buildup (odds ratio [OR], 1.03; 95% CI, 1.01-1.05) and were more likely to receive epinephrine (**ETR**) (OR, 1.03; 95% CI, 1.011.06)	Soller, 2019[9] (peanut, N=270)
SPT wheal size	In a multivariable logistic regression model, patients with a higher baseline SPT were more likely to receive epinephrine (**ETR)** (OR, 1.35; 95% CI, 1.051.75)	Soller, 2019[9] (peanut, N=270)
	No significant difference between those who continued or stopped treatment (P=0.62)	Nachshon, 2018[7] (peanut, N=111)
	Not associated with occurrence of adverse reactions following completion of OIT (P=0.087)	Elizur, 2016[16] (milk, N=197)
Maximum tolerated dose of food allergen	MITD not associated with occurrence of adverse reactions following completion of OIT (P=0.087)	Elizur, 2016[16] (milk, N=197)
	Starting dose: median 120 mg cow milk protein; range (10-7200 mg). ETRs were significantly more frequent in with a lower maximal tolerated starting dose (P <.0001).	Levy, 2014[14] (milk, N=280)

RCTs, CCTs AND SMALLER CASE SERIES

Baseline parameter	Outcome and correlation	Reference
Specific IgE blood levels	Patients who dropped out had higher egg sIgE serum antibody levels (P < 0.05).	Martin-Munoz, 2019a[20] (RCT **egg**, N=76 OIT, 25 control)
	Higher baseline sIgE levels were associated with OIT discontinuation or persistent reactions to OIT dosing. Optimal predictive cut-off levels were: egg-white sIgE: 9.41 kU/L; ovalbumin-sIgE: 6.49 kU/L and ovomucoid-sIgE: 8.85 kU/L.	Vazquez-Ortiz, 2014[54] (CCT **egg**, N=50 OIT, N=32 control)
	Fewer patients with lower sIgE levels (<3.5 kU/L) experienced adverse events (6/10, 60%) compared to 13/17 (76%) of patients with higher sIgE levels >3.5 kU/L (P=NR).	Garcia-Ara, 2013[43] (CCT, **milk**, N=36 OIT; N=19 control)
	Cox proportional hazards multivariate regression model identified sIgE ≥50 kU/L (HR 2.59, 95% CI 1.4-4.78, P=0.002) as independent risk factor for persistence of allergic reactions.	Vazquez-Ortiz, 2013[84] (case series, **milk**, N=81)

SPT	Peanut SPT was the only significant predictor of the rate of GI AEs, both before and after adjusting for sex, age, asthma, log peanut-specific IgE, atopic dermatitis, and AR. Rates of GI AEs increased 1.8-fold (95% CI: 1.4, 2.4, p-value: <0.001) for every 5 mm increase in SPT size.	Virkud, 2017[85] (retrospective pooled analysis of 3 RCTs, **peanut**, N=104)
Maximum tolerated dose of food allergen	Patients who dropped out had lower baseline threshold response dose (P < 0.05).	Martin-Munoz, 2019a[20] (RCT **egg**, N=76 OIT, 25 control)

Impact of baseline asthma status on safety outcomes

In many interventional (Bird, 2018;[5] Blumchen, 2019;[2] Longo, 2008;[10] Martin-Munoz, 2019;[20] Reier-Nilsen, 2019;[3] Tang, 2015;[4] Vickery, 2018[6]) and in some observational (Levy, 2014;[14] Nachshon, 2018;[7]) studies severe and/or poorly controlled or unstable asthma was an exclusion criterion for OIT.

Asthma-related outcomes in RCTs with N>50:

- Martin-Munoz, 2019a[20] (Spain – **egg**, age 6-9 years, N=101, asthma 30/101 [30%], severe or uncontrolled asthma at baseline excluded): Among all patients who started OIT (N=88) 8 (9.1%) withdrew during the build-up phase because of uncontrolled asthma.
- Blumchen, 2019 (Germany– **peanut**, age 3.2-17.8 years, N=62, uncontrolled asthma excluded, asthma: 65% placebo, 42% OIT) : After the course of OIT, no difference was found with respect to newly diagnosed atopic diseases (bronchial asthma, atopic dermatitis, allergic rhinoconjunctivitis) or worsening established atopic diseases at baseline.
- Vickery, 2018[6](**peanut**, poorly controlled asthma excluded, 53% of patients had asthma at baseline): Asthma exacerbation was recorded as an SAE in 2 OIT patients (4-17 years, N=372, 0.54%) and no placebo (N=124) patient.

Correlations between baseline asthma status and OIT safety / tolerability outcomes in large case series

Outcomes and Correlations	Proportion of patients with asthma	Reference
Compared to patients without asthma (N=93), patients with asthma (N= 101) had **more ETRs** during up-dosing (61% vs 34% of patients, mean ETRs per patient: 1.1 [SD 1.2] vs 0.4 [SD 0.7], P < .001) and at home (26% vs 4.2% of patients, mean ETRs per patient: 0.4 [SD 0.8] vs 0.1 [SD 0.5], P < .001).	101 patients with asthma, 93 no asthma	Elizur, 2015[73] (**milk**, N=194)
During the initial 10-day hospital-based "rush" phase, there was a **significant association** between the incidence of moderate to severe reactions and history of asthma (P=0.01). During OIT dosing phase at home, there was **no significant correlation** between the presence of asthma and/or viral wheezing and the total number of reactions or reactions requiring nebulised epinephrine.	asthma: 66%, viral wheezing: 34%	Barbi, 2012b[86] and Barbi, 2012a[87] (**milk,** N=132)
History of intermittent asthma **increased the risk** of **ETRs** (P = .035) and **ELORs** (P = .014) during dose escalation.	asthma: persistent: 43%, intermittent: 21%	Wasserman, 2018[8] (**peanut**, N=270)
While asthma was not significant in predicting rates of AEs overall, the presence of asthma significantly increased AE rates by 2.3 times during maintenance (P=0.03)	asthma: 44%	Virkud, 2017[85] (retrospective pooled analysis of 3 RCTs, **peanut**, N=104)
3 cases (2.3% of 130) of **life-threatening anaphylaxis** all in **teenage** boys with persistent asthma under suboptimal control, **high milk- or egg-specific IgE levels**, and **risk-taking behaviors**, including poor compliance to OIT and/or to asthma management plans	35% of patients (45/130) were on steps 3 to 4 of asthma treatment and 10% were adolescents (13-18 years old)	Vazquez-Ortiz, 2014[88] (**egg, milk,** N=130)

IMPACT ON QUALITY OF LIFE

<table>
<tr><th>Study – food allergen

Study design</th><th>OIT protocol variables</th><th>PRO data collection</th><th>Number and age of patients enrolled</th><th>PRO Results (n: number of patients with valid responses)</th><th>Factors that influenced QoL outcomes</th><th>Main findings and study limitations</th></tr>
<tr><td>Anagnostou 2014[1] - peanut

Crossover, open-label RCT</td><td>Target dose: 800 mg/d PP
Up-dosing interval: 2-3 weeks
Length of build-up phase: 26 weeks</td><td>FAQLQ-PF at end of OIT (26 weeks) – parent proxy</td><td>N=99 (49 OIT, 50 control)

Age: 7–16, median 12.4

FAQLQ-PF completed by parents of children of 7-12 yrs old</td><td>Median (range) change in FAQLQ-PF score from baseline to post-treatment:
OIT: (n=19): -1.61 (-4.87 to 0.24), P<0.001 (Wilcoxon signed rank test)
Control after crossing over to OIT (n=20): -1.41 (-4.83 to 1.38)</td><td>NR</td><td>OIT was associated with improvement in the parental FAQLQ-PF total score compared to baseline.

<u>Limitations</u>:
No comparator
Only parent report (no children),
Measured at one time point only
No information about the different domains of QoL</td></tr>
<tr><td>Dunn Galvin, 2018[89], Tang, 2015[4] – peanut

DBPCRT</td><td>Target dose 2000 mg/d PP
Up-dosing interval: 2 weeks
Length of build-up phase: 8 months
Maintenance dose and duration: 2000 mg/d PP for 10 months</td><td>FAQLQ-PF and FAIM (– parent proxy) at:
T0 (baseline)
T1 (end-of treatment, 18 months from T0 and before assessment of SU)
T3 (3 months post-treatment)
T4 (12 month post-treatment)</td><td>N=62 (31 OIT, 31 placebo)

Age: 1–10, mean 6</td><td>Mean (95% CI) change in FAQLQ-PF total score from T0 to:
<table>
<tr><td></td><td>OIT</td><td>Placebo</td></tr>
<tr><td>End of treatment (T1)</td><td colspan="2">No statistically significant improvement</td></tr>
<tr><td>T3: 3 months after T1</td><td>(n=24): +0.8 (0.001 to 1.7), P=0.05*</td><td>(n=27): 0.4 (-0.3 to 1.1), P=0.3</td></tr>
<tr><td>T4: 12 months after T1</td><td>(n=20): +1.3 (0.4 to 2.1), P=0.005*</td><td>(n=22): -0.6 (-0.8 to 0.7), P=0.8</td></tr>
</table>
Improvement in FAQLQ-PF score by ≥0.5 (MCID) 3 months post-treatment (T3): OIT: 77%; Placebo: 34%; Absolute risk reduction: 42.2%; NNT = 2.3 (95% CI 10 to 2)

Improvement (mean difference from baseline) by subscale:
<table>
<tr><td></td><td>T3</td><td>T4</td></tr>
<tr><td>FA</td><td>1.1, P = .003*</td><td>1.4, P = .001*</td></tr>
<tr><td>SDL</td><td>0.9, P = .09</td><td>1.2, P = .005*</td></tr>
<tr><td>EI</td><td>0.6, P = .1</td><td>1.1, P = .01*</td></tr>
</table>
Mean (95% CI) change in FAIM score from T0 to:
<table>
<tr><td></td><td>OIT</td><td>Placebo</td></tr>
</table></td><td>In the OIT group, 23 patients attained SU, 5 patients failed to achieve SU and 3 withdrew.

Patients who did not achieve SU (n=NR) showed no improvement in FAQLQ-PF scores at 3 or 12 months post-treatment (Mean Difference T0-T3 0.58, t = 1.05, P =0.4; Mean Difference T0-T4 0.2, t =0.23, P =0 .8).

Patients who achieved SU (n=NR) reported a significant improvement in FAQLQ-PF scores across all subscales at 3 (T3)</td><td>In a placebo-controlled trial, OIT was associated with clinically-important improvement of parental FAQLQ-PF scores compared to baseline 3 months and 12 months after the end of treatment, while there was no change in the placebo group.

Improvements were recorded in each of the 3 domains of the FAQLQ-PF, with the greatest improvement in the domain “food avoidance”.

Improvements were positively associated with achieving SU.

<u>Limitations</u>:
*Incomplete FU: by 12 months post-treatment, FAQLQ-PF data is only available from approx. 2/3 of the patients originally enrolled.
*No statistical analysis to compare change in FAQLQ-PF scores between the OIT and the placebo group.</td></tr>
</table>

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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>
<table>
<tr><td>End of treatment (T1)</td><td>(n=29): +0.8 (0.4 to 1.3), P=0.002*</td><td>(n=28): -0.2 (-0.5 to 0.2), P=0.3</td></tr>
<tr><td>T3: 3 months after T1</td><td>(n=24): +0.5 (0.04 to 1.0), P=0.03*</td><td>(n=27): -0.3 (-0.6 to 0.04), P=0.02</td></tr>
<tr><td>T4: 12 months after T1</td><td>(n=20): +0.4 (0.1 to 0.8), P=0.04*</td><td>(n=22): -0.13 (-0.4 to 0.1), P=0.3</td></tr>
</table>

Improvement (mean difference from baseline) by subscale:
<table>
<tr><th>Chance of:</th><th>T3</th><th>T4</th></tr>
<tr><td>Severe reaction, FAIM-2</td><td>1.0, P=.03*</td><td>0.8, P=.04*</td></tr>
<tr><td>Dying from allergen ingestion, FAIM 3</td><td>1.0, P=.1</td><td>1.2, P=.01*</td></tr>
<tr><td>Accidentally eating allergen, FAIM-1</td><td>0.9, P=.02*</td><td>0.7, P=.04*</td></tr>
<tr><td>Minimal improvement, FAIM-4</td><td colspan="2">P=0.3</td></tr>
</table>
</td>
<td>and 12 (T4) months post-treatment (Mean Difference T0-T3 1.3, t = 2.8, P = .01; Mean Difference T0-T4 1.8, t = 2.7, P = .001).</td>
<td>*Only parental report (no children)
*Placebo-controlled (up to T1?): Subjective impact of OIT may not be fully captured in the absence of assurance of successful treatment</td>
</tr>
<tr>
<td>Blumchen, 2019[2] - peanut

DBPCRT</td>
<td>Target dose: 125-250 mg PP
Build-up interval: 2 weeks
Build-up duration: up to 14 months
Maintenance dose and duration: median: 125 mg/d for 8±2 weeks</td>
<td>FAQLQ-PF (for mothers of children age 3-12) at a median of 9.5 weeks (IQR, 5-15.3) after final OFC

FAQLQ-CF (for children age 8-12) at a median of 11 weeks (IQR, 7-16) after final OFC</td>
<td>N=62 (31 OIT, 31 placebo)

Age: 3.2-17.8, median 6.8

FAQLQ-PF: OIT: 27, placebo: 21

FAQLQ-CF: OIT: 11, placebo: 9
BOT: OIT : 50 mothers of children (3-12 years), 21 children (8-12 years)</td>
<td><u>FAQLQ-PF (mothers)</u>
Total score: median change from baseline not statistically significant in both OIT (n=20) and placebo (n=18) groups
No statistically significant change in all sub-scales
No statistically significant difference in changes between OIT and placebo.

<u>FAQLQ-CF (children age, 8-12 years)</u>
Total score: median change from baseline statistically significant in OIT group (n=9): -1.0 [IQR -2.7 to -0.5]; not statistically significant in placebo group (n=8): -0.1 [IQR-1.2-0.7], but difference between OIT and placebo not statistically significant (P=0.1)
By subscale, statistically significant improvement from baseline for:
• RAE (-2.0 [IQR -3.3 to -0.9])
• EI (-1.8 [IQR -2.8 to -0.9]), and
• AA (-1.9 [-3 to -0.1]),
but not for DR.
Changes statistically different from placebo only for “risk of accidental exposure” and “emotional impact” (P=0.02 for both)</td>
<td>Not reported</td>
<td>In a placebo-controlled RCT, at approx. 3 months post-treatment there was no significant change of parental FAQLQ-PF scores compared to baseline or to placebo. However, children (age 8-12) in the OIT group reported clinically important and statistically significant improvements from baseline in the FAQLQ-CF total score and in all domains, except “dietary restrictions”. There were no significant changes from baseline in the children’s placebo group; differences between the two groups were not statistically significant, except for “risk of accidental exposure” and “emotional impact”.

<u>Limitations</u>:
*Incomplete FU
*Small sample size, particularly for the children (20 in total)
*Outcomes measured at one time point only
*Placebo-controlled: Subjective impact of OIT on QoL may not be fully captured in the absence of assurance of successful treatment</td>
</tr>
</table>

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<tr>
<td>Reier-Nilsen, 2019b[90] and 2019a[3] - peanut

RCT-open label</td>
<td>Target dose: 5000 mg PP
Build-up interval: 2 weeks
Build-up duration: 50-78 weeks
Maintenance dose and duration planned: 5000 mg/d for 36 months; observed: mean 3322 mg PP (range 350 to 5000)</td>
<td>PedsQL 4.0 (parents and children) at enrolment (Y0), after 1 year (end of up-dosing) (Y1) and after 2 years (Y2) of OIT

FAQL-PB (parents)</td>
<td>N=77 (57 OIT, 20 control)

Age: 5-15, median 10.1 OIT and 8.9 control</td>
<td>Mean (95% CI) PedsQL 4.0 scores from baseline to Y2:
<table>
<tr><th>OIT (n=39)</th><th>Control (n=20)</th><th>Between groups</th></tr>
<tr><td>Children</td><td></td><td></td></tr>
<tr><td>from 82.1 to 86.7: +4.4 (0.5, 8.3) P<.0001*</td><td>from 83.4 to 82.2: -0.9 (-7.9, 6.11), P=0.8</td><td>P= 0.12</td></tr>
<tr><td>Parents</td><td></td><td></td></tr>
<tr><td>from 78.7 to 83.7: +9.3 (4.3, 14.3) P<.0001*</td><td>from 81.7 to 82.1: +0.4 (4.3, 14.3), P=0.9</td><td>P=0.02*</td></tr>
</table>
Parents' FAQL-PB improved significantly among both the OIT-group by -9.9 (95% CI -14.6, -5.3) (P<0.0001) and the control group by -9.4 (-15.3, -3.6) (P=0.004) from Y0 to Y2, with no significant difference between groups (P=0.57)</td>
<td>In multivariate robust regression analysis, none of the factors examined (age, gender, maintenance dose, perceived burden of GI AEs and perceived burden of taste/amount) were associated with a change in PedsQL4.0 (child), PedsQL4.0 (parent) or FAQL-PB (parents) scores.</td>
<td>Mean generic PedsQL 4.0 scores improved significantly from baseline to Y2 in both children and parents, while no significant difference was seen in controls. Compared to controls, the improvement was significantly different among parents only.

<u>Limitations</u>:
*Incomplete FU: Data not available for 32% (18/57) of the children who discontinued OIT
*Small sample size
*Children completed a generic QoL instrument only
*No information about the different domains of QoL</td>
</tr>
<tr>
<td>Epstein Rigbi, 2019[91] - milk, peanut, egg, sesame, or tree nuts

Prospective cohort study</td>
<td>Target doses (mg protein): Milk: 7,200; egg: 12,000; peanut: 3,000; sesame: 5,000; tree nuts: 4,000
4 weeks (1 month)
Planned: 8 months; observed: mean 7.8 (SD 5.7) months
Maintenance (mg protein): Peanut, sesame, and</td>
<td>FAQLQ-PF (parents) at OIT initiation, mid up-dosing (4 months of OIT), after reaching maintenance (end of treatment), and 6 months into maintenance</td>
<td>N=191 (consecutive patients initiating OIT), 48 control group (matched for age and allergenic foods)

Age: 4-12, mean 6.3</td>
<td>Mean scores in 175 (of 191, 92% follow-up) patients (158 had reached full, 14 partial maintenance dose, 3 discontinued [failed OIT])
<table>
<tr><th>FAQLQ-PF</th><th>OIT start</th><th>Reaching maintenance or treatment cessation</th><th></th></tr>
<tr><td>Total score</td><td>3.69</td><td>3.19</td><td>P < .001*</td></tr>
<tr><td>EI</td><td>3.66</td><td>3.32</td><td>P=0.001*</td></tr>
<tr><td>FA</td><td>3.90</td><td>3.32</td><td>P<0.001*</td></tr>
<tr><td>SDL</td><td>3.50</td><td>2.94</td><td>P<0.001*</td></tr>
</table>
No significant changes in the control group (n=48) between 2 time points (mean interval 13.3 [SD11.2] months) in any of the domains or in the total score.

The 14 patients who reached a partial maintenance dose (150-2700 mg protein) experienced a significant improvement in mean FA (P=0.001), SDL (P=0.036), and total (P=0.015), scores, but not for EI (P=0.12) from start of OIT to maintenance. The 3 patients who failed OIT reported no significant change from the start of OIT to treatment cessation (range, 2.6-4.3 months).</td>
<td>In linear regression analysis, a single food allergy (P<0.001 SDL and total P=0.01EI, P=0.003 FA), and a worse baseline FAQLQ-PF score (P<0.001, all domains and total) predicted a greater improvement in FAQLQ-PF scores from start to maintenance/ cessation of treatment.
History of anaphylaxis was associated with greater improvement in single-factor analysis (<.05)</td>
<td>In a prospective cohort study, parents' FAQLQ-PF scores significantly improved in all dimensions from OIT initiation to reaching full and/or partial maintenance, whereas there was no change in controls.

Worse baseline QOL, a single food allergy, and younger age predicted greater QOL improvements.

Among the subset of patients whose FAQLQ-PF total score deteriorated from baseline to mid up-dosing, FAQLQ-PF scores returned to near-baseline upon reaching maintenance.

Additional significant improvement in QOL was observed 6 months after reaching maintenance.</td>
</tr>
</table>

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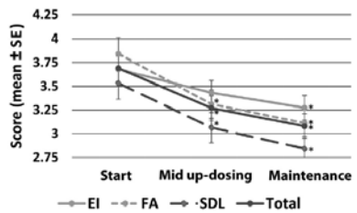
<tr>
<td></td>
<td>tree nuts: 1200; milk: 3600; egg: 6000</td>
<td></td>
<td></td>
<td>Among 85 patients (of 96 eligible for mid-point assessment, 88.5% follow-up) who completed the FAQLQPF at mid up-dosing, a statistically significant improvement was seen between the start of OIT and mid-up-dosing for FA, SDL, and the total score but not for the EI domain:
 

Among the subset of patients whose FAQLQ-PF total score deteriorated (increased by > 0.5) from baseline to mid up-dosing (n=NR), FAQLQ-PF scores returned to near-baseline upon reaching maintenance.

Mean FAQLQ-PF scores among 93 OIT patients with 6-months of maintenance (of 105, 88.6% follow-up)
<table>
<tr><th></th><th>Baseline</th><th>Reaching maintenance</th><th>6 months of maintenance</th></tr>
<tr><td>Total score</td><td>3.55</td><td>3.23</td><td>2.55</td></tr>
<tr><td>EI</td><td>3.55</td><td>3.37</td><td>2.87</td></tr>
<tr><td>FA</td><td>3.78</td><td>3.32</td><td>2.55</td></tr>
<tr><td>SDL</td><td>3.33</td><td>2.99</td><td>2.28</td></tr>
</table>
Significant differences were found for FA, SDL, and total score between start and maintenance and for all domains from maintenance to follow-up.

The 14 patients reaching partial maintenance reported had worse FAQLQ-PF scores at baseline and reported significant improvement in the FA (P=.001) and SDL (P=.036) domain and the Total score (P=.015)</td>
<td><u>Not significant</u>: asthma, food allergy treated, SHTD (starting dose), reactions during treatment, duration of OIT.
<u>Borderline significant</u> for EI and SDL: younger age

Among the 158 patients who reached full desensitization, younger age predicted a greater improvement in the FAQLQ-PF scores. (EI, P=0.029, FA, P=n.s., SDL, P=0.021, total score, P=0.042)</td>
<td><u>Limitations</u>:
*Not randomized: there may have been significant differences between controls and OIT groups
*Only parent-reported QoL measures</td>
</tr>
<tr>
<td>Factor, 2012 [92] – peanut

Case series</td>
<td>Build-up target: 450 mg PP /d</td>
<td>At baseline and on achieving the maintenance</td>
<td>N=100

Age: 5-18 (85 aged 5-</td>
<td>Significant improvement in QoL in all domains (AA, DR, RAE, EI, FA, and SDL) with the exception of the EI domain on the teens' survey.</td>
<td>NA</td>
<td><u>Limitations</u>:
*No control group
*No analysis</td>
</tr>
</table>

<table>
<tr><th>Study – food allergen

Study design</th><th>OIT protocol variables</th><th>PRO data collection</th><th>Number and age of patients enrolled</th><th>PRO Results (n: number of patients with valid responses)</th><th>Factors that influenced QoL outcomes</th><th>Main findings and study limitations</th></tr>
<tr><td></td><td>Build-up interval: 2 weeks</td><td>dose: Parents of 5 to 12-year-old children: FAQLQ-PF
8-12-year-old children: FAQLQ-CF
Teens (age 13-18): FAQLQ-TF</td><td>12, 35 aged 8-12, and 15 aged 13-18)</td><td>QoL significantly improved (P<.02) on all 30 questions when parents assessed their children 5 to 12 years old.

When children (8–12 years old) and teens assessed themselves, QoL improved (P<.05) on 22 of 24 questions and 12 of 18 questions, respectively.

Percentage of responses than decreased by ≤ 1 point by domain:
<table><tr><td>Parents (n=76)</td><td>FA: 65.7%, SDL: 64.4%; EI: 55.1%</td></tr><tr><td>Children (n=32)</td><td>DR: 69.7%, RAE: 65.2%; AA: 62.7%; EI: 56.5%</td></tr><tr><td>Teens (n=14)</td><td>AADR: 71.9%, RAE: 67.9%; EI: 49.4%</td></tr></table>
See Figure bellow</td><td></td><td></td></tr>
</table>

n: number of patients with FAQLQ-PF data; N: number of patients enrolled; NA: not available; NR: not reported; T3: 3 months after build-up phase, T4: 12 months after build-up phase

FAIM: Food Allergy Independent Measure: FAIM total score is based on 4 main questions, with a response scale from 0 (no chance) to 6 (very great chance): FAIM-1: chance of accidental exposure, FAIM-2: chance of a severe reaction on food exposure, FAIM-3: the chance of dying from food exposure and FAIM-4: chance of a child effectively treating him/herself or receiving effective treatment, following a food allergic reaction. Additional questions 5 and 6 ask (respectively) how many foods are avoided because of FA (categorized as single, 2, multiple >2) and how much FA limits the type of activities that the child can take part in. A reduced FAIM score indicates an improvement in the parent's perception of the chance of an adverse outcome for their child with FA.

FAQL-PB: Food Allergy Quality of Life–Parental Burden: 7-point Likert scale (1 = not troubled, 7 = extremely troubled) for each question are summated, reporting the sum ranging from 17-119.

FAQLQ-PF: Food Allergy Quality of Life—Parent Form: for parents of children age 0-12 years: 7-point Scale (0- minimal impairment to 6 –maximal impairment), averaged over 3 areas with equal weighting: Emotional impact (EI), Food anxiety (FA), and Social and dietary limitations (SDL). The minimal clinically important difference (MCID) for FAQLQ-PF is 0.5.

FAQLQ-CF: Food Allergy Quality of Life—Child Form: for children age 8-12 years: 7-point Scale (1-not troubled to 7 –extremely troubled): 4 domains (24 items): Allergen avoidance (AA), Risk of accidental exposure (RAE), Emotional impact (EI), Dietary restrictions (DR). The minimal clinically important difference (MCID) for FAQLQ-CF is 0.5.

MCID: Minimally clinically important difference

PedsQL 4.0: Pediatric Quality of Life Inventory Version 4.0: 5-point Likert-scale (0=never, 4=almost always) for 8-18 year-olds, and a simplified 3-point scale for 5-7 year-olds. The 13 items are reverse-scored (0=100, 1=75, 2=50, 3=25, 4=0) reporting the mean sum of each item. The minimal clinically important difference (MCID) is ≥5.3 for child self-report and 5.5 for parental proxy report.

Perceived treatment burden: VAS-form: 3 domains: GI related AEs, taste and amount of daily peanut-dose, and time spent on OIT, range of VAS:0=no burden, 10=massive burden

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